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THE SURFACE TREATMENT OF BURNS*

A COMPARISON OF RESULTS OF TANNIC ACID, SILVER NITRATE, TRIPLE DYE, AND VASELINE OR BORIC OINTMENT AS SURFACE TREATMENTS IN 150 CASES

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DURING THE PERIOD August 6, 1942, to March 10, 1943, there were 212 cases of burns given surface treatment by one of three standard methods at the Boston City Hospital. All of these cases were serious enough to warrant admission to the wards of the hospital. Of them, 109 came from the "Cocoanut Grove" disaster and 103 at other times. Certain cases have been excluded from the present report because there is no way of using them in evaluating the efficiency of surface treatment. The largest group of these exclusions are 33 "Cocoanut Grove" cases, and four other cases that had severe respiratory involvement as well as external burns, and whose death was so largely contributed to by the respiratory factor that evaluation of surface treatment was impossible. All of these deaths occurred within 12 days after injury.

Other groups excluded are patients who were discharged early and "lost" at a time when the depth of the burn could not be estimated, and a few cases who came to the hospital over 48 hours after their burn and cases where other than standard primary surface treatments were used. There remain 150 cases that form the basis of this report. Experimental surface treatments were used on certain areas of some of these cases. The results of the treatments to these areas are not considered in this report. No experimental primary treatments were used on any of the cases from the "Cocoanut Grove" fire.

Table I shows the age and sex distribution of these cases.

The sporadic cases of burns admitted to the wards of this hospital are due to many agents and the patients are of all ages from infancy to extreme old age. Usually about half the patients admitted are children and half of

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TABLE I

STUDY OF SURFACE TREATMENT

DISTRIBUTION OF CASES BY AGE AND SEX

	Male		Female		Total		
Ages	C. G.*	Other	C. G.*	Other	C. G.*	Other	Total
0–4	0	17	0	2	0	19	19
5–9	0	10	0	4	0	14	14
10–19	2	10	2	3	4	13	17
20–29	21	1	16	1	37	2	39
30–39	10	4	8	5	18	9	27
40–49	2	9	0	4	2	13	15
50–59	1	5	0	3	1	8	9
60–69	0	2	0	3	0	5	5
70–79	0	0	0	1	0	1	1
Unknown	1	1	2	0	3	1	4
Total	37	59	28	26	65	85	150

*Cases burned in the Cocoanut Grove disaster.

them adults. About half the burns are caused by scalding with hot aqueous fluid (water, tea, coffee, soup, *etc.*). About 40 per cent are flame burns. The remainder are burns from miscellaneous causes such as hot oils and greases, molten metal, hot nonmolten metal, acids, other chemicals and electric flashes, *etc.* The patients are usually from the poorer economic strata of the community and a fair percentage are poorly developed, poorly nourished, and anemic. Adults burned in bed or whose clothing has been on fire are frequently intoxicated and many of them are in a state of chronic alcoholism.

In sharp contradistinction to the usual group of patients were those burned in the Cocoanut Grove disaster. They were mostly young adults in excellent physical condition. Very few, if any, were under the influence of alcohol. It has been estimated that the average patient in this group had consumed the equivalent of two cocktails (25 cc. of pure alcohol) during the three hours preceding the fire. There was only one known chronic alcoholic among these cases. All of these burns were flame burns and none of them scalds.

CLASSIFICATION OF BURNS

For the purpose of this report only second and third degree burns are discussed. Second degree burns include all burns, no matter how deep, that destroy only a part of the epithelium. Third degree burns include only those that destroy the whole epithelium. The appearance of the burn on admission and for some time thereafter, is frequently not a reliable guide to the depth of the burn. However, many small blisters, slight edema of the skin, weeping of broken blebs with a pinkish color of the corium under the blebs, indicate the presence of a second degree burn. On the other hand, charring, dry dead white, or brownish, leathery appearance without edema below it, indicate the presence of a third degree burn. There is, however, a rather large group of cases that cannot be finally classified until they are either well on toward healing in the case of second degree, or granulating in the case of third degree (Fig. 1 A-D). This study is based entirely on a classification of the cases at a time after the injury when an accurate estimate as to

depth and of the areas involved in each depth could be made. The percentages of body area involved were calculated by the use of Berkow's[1] formula.

PRELIMINARY TREATMENT

On entering the accident floor the patients were seen by an admitting physician, given suitable doses of morphine, and undressed. Ordinarily, patients without shock were sent to the operating room for prophylactic plasma therapy, if needed, and initiation of surface treatment. A few very severely burned patients were sent to the "shock room" of the accident floor and treated there until death or beginning recovery. The Cocoanut Grove patients were given morphine in the accident floor as usual but they were not undressed until they arrived in the operating room or the wards. About 35 of these patients were treated in the operating rooms. The rest were placed in bed in the wards and treated there, because of limited operating room facilities.

TANNIC ACID-SILVER NITRATE TREATMENT

The tannic acid-silver nitrate treatment was used only on burns of the body, legs, and arms. A rapid tanning after removal of loose débris and washing was made according to the accepted treatment described in the U. S. Army Manual.[2] Freshly dissolved 10 per cent tannic acid solution in water was applied to the whole area. Then the remainder of this solution was added to an equal amount of 10 per cent silver nitrate solution making a solution of 5 per cent of each. This was applied at once and every half hour for four applications. Anesthesia for the cleaning was used in some cases, particularly in young children. After the fifth application of the tanning solution, a dry, firm, rather thin, moderately elastic eschar was formed. A cradle with moderate heating by electric lights was used to promote the drying. Sterile sheets were not used. If the eschar remained intact and clean it was allowed to remain until it came away spontaneously. This occurred only in a few second degree burns. It was found that these eschars were relatively impervious to moist solutions once they had dried out. In all the third degree cases signs of softening with infection under the eschar appeared in from four to eight days (Fig. 1 A-D). The eschar was excised over such areas and secondary treatment initiated.

TRIPLE DYE TREATMENT

From the beginning of the study until the night of the Cocoanut Grove disaster, no dye treatments were used. But for many years previously, as a result of the important investigations made by Aldrich,[3] "triple dye" had been the treatment most used in this hospital for severe burns. For two reasons it was used extensively on the patients from the Cocoanut Grove. Supplies of silver nitrate were rapidly exhausted and many staff surgeons not connected with the Burn Assignment were called in and were permitted to use the dye treatment with which they were most familiar. In the six weeks following the disaster a few additional cases were also treated in this way.

Triple dye is a water solution containing gentian violet, methyl green and acriflavine. It is claimed that when properly used it has bacteriostatic properties against both gram-positive and gram-negative organisms. Aldrich[4] has recently advocated its use without previous cleaning unless gross soiling of the burn has occurred. In the present cases a moderate amount of cleaning (breaking of blisters and removal of loose sheets of broken epidermis) was carried out in many cases. In some, soap and water washing of the surface was also done. On the night of the disaster many cases were treated with applications of this dye to burns of all parts of the body including hands and face. During the period of application the patient was protected from the contact with bed clothing by a cradle with lights and the solution was brushed on with a sponge every one-half to one hour. An eschar was formed much more slowly than with tannic acid-silver nitrate, and applications were continued up to 24 hours in most cases and to 48 hours in some (Fig. 3 A-E).

These eschars are much more sensitive to moisture than the tannic eschars. They soften and break down rapidly not only on application of ointments or saline dressings but also as a result of lying on them for a very few hours. If softened as a result of moisture without grease, they may, however, be repaired by a further application of the dye followed by a further period of drying. Even after infection has been established on the granulating surface under the eschar, the surface may be wiped and redyed. Such a secondary eschar is not as satisfactory as the original one but it does cover the open surface to some extent. However, such areas must be inspected daily and collections of pus unroofed and the granulations redyed.

1A. Flame burn after cleaning and before tanning. Note that the apparent depth of the burn of the left buttock and of the right calf seem to be equal. The small wounds were biopsies.

1B. Fourth day, after tannic acid-silver nitrate. Close inspection shows a "blister" on medial edge of right buttock. The fluid from this cultured colon bacilli.

1C. Twelfth day. The eschar was excised daily where it softened and saline dressings were applied. The infection became mixed and later the child lost much weight. Note the similar appearance of the necrotic tissue under the eschar of the two buttocks.

1D. Twenty-eighth day. The left buttock is healed indicating that this area was a second degree burn, but the right burn was third degree even on the calf. In this case the first sure evidence of depth of burn was after three weeks. Recovery without deformity followed Thiersch grafting. Final determination of area of burn was second degree, 6%, third degree, 10%. The burn extended beyond the limits seen on any of these photographs.

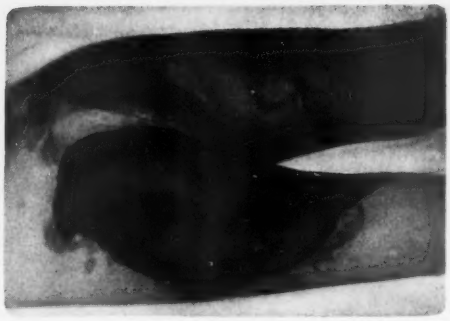
2A. Seventh day, at the first change of dressing after treatment with vaselined gauze and a firm voluminous dressing.

2B. Twelfth day. The same treatment was continued.

2C. Twenty-third day. Small Thiersch grafts put on part of the granulations as an experiment.

2D. Twenty-ninth day. The grafts are alive and remained so. Further grafting was done later. Final determination of area of burn, second degree, 4%, third degree, 16%.

1A



1B

1C

1D

2A

2B

2C

2D

FIGURE 1.—M. F., age 10, admitted August 24, 1942.
FIGURE 2.—F. P., age 40, admitted February 3, 1943

MIXED TANNIC ACID AND DYE TREATMENT

In some of the Cocoanut Grove cases eschars were started with tannic acid-silver nitrate and completed with triple dye. This procedure was never used at any other time. Since such eschars seem to have more of the physical characteristics of the underlying tannic acid-silver nitrate than of the overlying triple dye, they are classed with the other tannic acid eschars.

OINTMENT TREATMENT

Autoclaved strips of fine-mesh gauze impregnated with vaseline and of wide-mesh scrim impregnated with boric acid ointment were used for the treatment of many areas of burns of the hands, face, feet, or genitalia of all patients otherwise treated with tannic acid-silver nitrate and of some patients treated with triple dye. Such ointment dressings were also applied to the bodies, arms, and legs as the only treatment of other patients (Fig. 2 A-D). Until after the experience at the Massachusetts General Hospital in treating other victims from the disaster became known,[5] burns treated in this manner were always débrided and cleaned before the application. Commencing in February, many of the cases were treated with vaseline without cleaning (Fig. 2 A-D). Pressure dressings of the type and efficiency described by Allen and Koch[6] were not used except for a few cases. Burns on the faces of some cases were treated by the application of vaseline or boric acid ointment unsupported by gauze of any kind. No difference in results have been observed distinguishing vaselined gauze from boric acid ointment. For the purpose of this study they are both tabulated under the heading "ointment."

SECONDARY TREATMENT

Vaselined gauze, boric ointment gauze, and saline, boric acid, or weak Dakin's solutions were the chief applications used in secondary treatment. In general, if good progress was being made with ointment dressings these were replaced at intervals of five to seven days until healing or the necessity for grafting was demonstrated. When the time for grafting approached a change to frequent moist dressings was made. Tannic acid eschars on deep burns frequently had to be removed at the end of the first week because of underlying infection. This was done in part by application of vaselined gauze or wet dressings. Many of the triple dye eschars were also removed in the same way at an early date. One patient in the Cocoanut Grove group, with a 20 per cent area of third degree burn, became very toxic, and it was thought that infection under the eschar was responsible. The eschar was being removed by vaselined gauze and saline dressings. At one dressing an overenthusiastic application of sulfanilamide powder resulted in typical sulfanilamide toxemia, with cyanosis. The plasma sulfanilamide level rose to 20 mg. per cent. Sulfanilamide powder was utilized in this manner only in this one case. In a few cases triple dye eschars were retained for several weeks, repairing any softened areas by redyeing (Fig. 3 A-C). This was

done only in patients that were so toxic that any change in treatment was felt to be dangerous.

All the patients with second degree burns suffered very little pain at any time following the first dressing, but most of the patients with third degree burns suffered greatly and became extremely sensitive to very slight trauma. This was especially true if wet dressings were allowed to become partially dry before changing. Some of the more severely burned patients were given morphine or general anesthesia at the time of some dressings. Because of pain a few patients were treated with sulfathiazol ointment, cod liver oil ointment and with "eusol"* solution primarily because of the good psychic effect that frequently follows a change of method. Some of the patients felt that these changes were beneficial as far as pain was concerned. No other benefit was observed.

A few cases with deep burns of the hands and forearms had slow separation of their sloughs. Their dressings were often very painful. In eight instances Bunyan envelopes†[7] were used as a means of supplying irrigation with saline solution or Dakin's solution. This method of treatment at this stage was successful in relieving a large degree of the pain in six out of the eight patients so treated. It has been recommended that the fluid be drained periodically. The cycles used varied, with the period of filling from 20 minutes to one hour and the empty period from two to four hours. Bunyan advocated the instillation of oxygen when the fluid was out in order to keep the membrane from contact with granulations. Most of our patients preferred not to have the oxygen instilled, as they were more comfortable without it in spite of the fact that the upper surface of the empty bay lay against the granulation tissue.

Splints were used early and freely in burns of the forearm and hand and occasionally for burns of the legs. The splints served to reduce the amount of pain and to rest the part by reducing the possible range of motion in the wrists and finger joints and also served to prevent contractures. In the early days after the Cocoanut Grove disaster, a straight anterior splint with the fingers extended was applied to many patients with deep burns of the posterior aspect of the hand and fingers. From the point of view of pain, this was certainly useful, but it is very doubtful that this form of splinting should be used in the future, because posterior contractures occur rapidly. Splinting in the neutral position may avoid part of this difficulty.[8, 9]

* Edinburgh University solution—equal parts of liquid petrolatum and a solution containing 1.25 per cent boric acid and 1.25 per cent calcium hypochlorite, emulsified immediately prior to use.

† These envelopes were kindly furnished by the Union Carbide and Chemical Corporation.

THE RELATION OF SHOCK AND HEMOCONCENTRATION TO SURFACE TREATMENT

Death from shock occurred in only one instance. This was in a patient with flame burns of 60 per cent of her body surface treated with tannic acid-

silver nitrate, who received a very inadequate dose of plasma, 1000 cc., quite large amounts of electrolyte solutions intravenously, and died at 22 hours.

Tannic acid-silver nitrate treatment controls surface leakage after it has been applied. Triple dye controls it more slowly. Vaselined gauze without pressure allows it to continue until it stops spontaneously. None of these treatments controls the subcutaneous loss of plasma which may be very large in amount and in fact may be much more important than the surface ooze. It is possible that well applied pressure dressings do control this loss and the loss through the surface to some extent,[10] particularly on the hands and forearms. Subcutaneous edema is most marked in the face and very difficult to control by pressure.[5] No effort was made to control it in this group of cases. The maximum swelling was seen at 24 hours. At seven to ten days it had disappeared entirely.

Careful washing was used regularly up to the night of the disaster for all cases. After it, it was used less and less, and given up entirely as soon as the good results of ointment and pressure treatment without scrubbing that were secured by Cope[5] became known. That cleaning itself can add to shock is understandable. First, it may entail a fair amount of manipulation and either pain or anesthesia, both of which are harmful. But most important, it frequently may start up a very visible surface exudation that had previously ceased. Further discussion of these important matters will be made in other articles.[11, 12]

3A. A very satisfactory "triple dye" eschar on the thirteenth day. How much of this burn is third degree?

3B. On the 10th day, saline dressings were started. This is its condition on the 21st day.

3C. Hands on the 32nd day. The original treatment of the two hands was the same. The eschar was deliberately removed from the left hand but not from the right by wet dressings started one week before this picture. This indicates that readiness for grafting in eschar-treated cases depends to some extent on the time that secondary treatments are started.

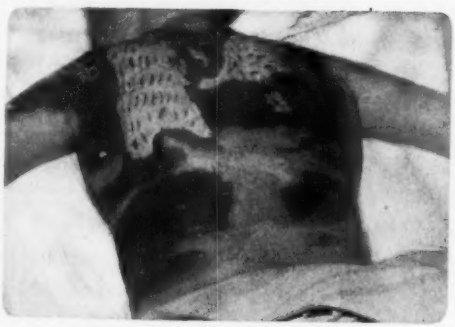
3D. Back on the 37th day. This area was ready for grafting prior to this time but delay was necessary because of poor general condition.

3E. Back on 64th day, 17 days after a completely successful grafting of part of the area. Note, here also, that whether a burn was second or third degree could not be told until the eschar was removed. Final determination of area of burn, second degree, 10%, third degree, 20%.

4A. After cleaning. This burn was due to hot water.

4B. On the fifth day. Notice that much blistering had occurred under the dressing. This indicated a gentle débridement at an early hour. It also indicates that it may be as difficult to distinguish early between a first and a second degree burn as between a second and a third degree burn. This dressing was removed unusually early in order to see the results of treatment.

4C. Eleventh day. The burn is nearly healed and was healed and dry on the fourteenth day. Pigment returned later. This was a second degree burn of rather superficial nature and of remarkably even depth. Final determination of area of burn, second degree, 20%, third degree, 0%.



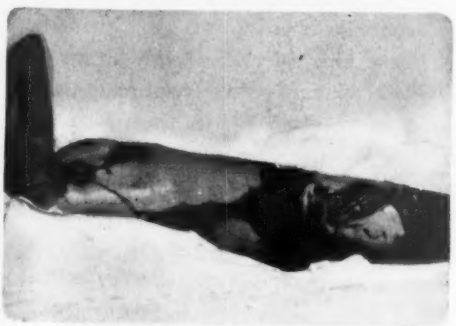


FIGURE 3.—A. D., age 30, admitted November 28, 1942.
FIGURE 4.—P. F., age 20, admitted January 21, 1943.

POSSIBLE TOXIC EFFECTS OF SURFACE AGENTS USED

Very recently instances of tannic acid poisoning have been reported.[13, 14] In general, such reports have incriminated slow methods of tanning rather than the rapid tanning used in these cases. No instances of central necrosis of the liver have been seen in any of the cases in this series coming to autopsy. Neither triple dye, boric acid ointment, nor vaseline have ever been shown to be toxic. One patient, mentioned above, had a temporary toxic level of sulfanilamide from surface application of this drug.

One death only in this series occurred in the interval of time during which Wilson[15] considers deaths from burns to be toxic deaths. This patient was treated with tannic acid-silver nitrate. She died on the fifth day with thrombocytopenic purpura, anemia, edema, azotemia, and anuria.

INFECTION IN SECOND DEGREE BURNS

There were 75 cases in the present series having only second degree burns. These varied in area from just under one per cent to 20 per cent of the body surface. Seven were treated with tannic acid-silver nitrate alone, 59 with vaseline alone, one with triple dye, and eight with triple dye on some areas and vaseline on others. Many of these patients, burned in the Cocoanut Grove disaster, had additional pulmonary damage. About half of the whole group had temperatures of 101.0°F., or more, some time in the first three days, and a few reached 103.0°F., for a few hours during this time. The other half had normal temperatures at all times. All of the cases with an early rise had essentially normal temperature charts from the third day to complete healing of the burn with five exceptions. Two children had fever associated with upper respiratory infections and one child had a febrile reaction from the administration of serum. One unexplained rise of temperature to 105°F. on the fourth day occurred in a seventy-year-old woman. It is presumed that this fever, which lasted for 48 hours and suddenly receded, resulted from infection with a new organism that entered the burn, although there was no sign of cellulitis, lymphangitis or of intercurrent infection. In one man the temperature rose on the 14th day to 102.0°F., just before healing became complete, and this reaction was associated with lymphangitis. A culture from the burn at this time demonstrated a beta hemolytic streptococcus. These two infections both occurred in vaseline-treated cases and both subsided promptly on treatment with sulfadiazine, and did not delay the healing of the burns. In the first case no prophylactic sulfadiazine treatment had been given, but the second case had had full doses of sulfadiazine for eight days. Half of all these cases had been given oral sulfadiazine for 8 to 21 days beginning at 12 to 36 hours. This incidence of three per cent of clinical infection in 67 cases treated in whole or in part by vaseline, and of no infection in seven tannic acid treated cases, and eight treated with triple dye, indicates these treatments are safe treatments from the point of view of infection in second

degree burns even when sulfadiazine is not given as a precautionary measure. It also indicates that infection was not an important problem in these cases with second degree burn only. The patient with the largest area of purely second degree burn (scald) had 20 per cent involvement. Treatment was with vaselined gauze in large part and an experimental treatment in smaller part. There was never any fever (Fig. 4 A-C).

HEALING OF SECOND DEGREE BURNS

The end-point of healing in second degree burns, used as a criterion in the various cases treated, is the time when intact epithelium without crusts or sloughs adhering to it covers the whole area of the burn. Table II presents this data for the cases in this series. More areas are tabulated than there are cases because in many instances more than one kind of treatment was used and different areas had different end points. For instance, in an extreme case four areas might be studied on one patient. Second degree areas in cases also having third degree burns are included.

TABLE II

STUDY OF 150 BURNS

HEALING OF SECOND DEGREE BURNS

Area Involved	Face		Back		All Other	
Treatment	No. of Areas	Av. Time (Days)	No. of Areas	Av. Time (Days)	No. of Areas	Av. Time (Days)
Ointment.....	68	11	7	19	90	15
Tannic-silver.....	0	—	6	27	19	24
Triple dye.....	4	13	8	25	19	16
All treatments...	72	11	21	23	118	18

Table II shows that irrespective of treatment, healing of the face is rapid, of the back, slow, and the rest of the body, intermediate. It does not show any shorter healing time of those burns treated with ointment over that obtained with triple dye except, possibly, in burns of the back. The slight advantage of ointment over tannic acid in length of healing time extends to all areas studied.

Reasons for the rapid healing of the face and slow healing of the back can only be speculative. In favor of rapid healing of the face is a copious circulation, possible conditioning of the skin to thermal trauma by exposure, a firm connection to the underlying tissues, numerous subcutaneous glands of epithelial origin, and relative freedom from trauma during the period of healing. The main reasons the back may heal slowly are that the skin is thick and, therefore, a burn which is deeper than is possible in other areas may still be a second rather than a third degree burn, and that, during healing, trauma (from lying on the back) may be frequent. These burns cannot strictly be compared with those of other areas.

Further analysis of the available data permits the following additional statements to be made:

1. Areas of pure second degree burn heal no more rapidly than the areas of second degree burn associated with areas of third degree burn.

2. Areas of second degree burn heal as rapidly when extensive as when small, within the limit of size observed (20 per cent of body area).

3. Second degree burns of the anterior part of the body, buttocks, thighs, legs, feet, arms and hands all give the same range and average time of healing. The number of cases of burns of the palms of the hands and soles of the feet is too limited to allow any judgment as to healing of this specialized skin.

4. The range of time of healing varies directly with the depth of the second degree burn. This range is narrow for the face, five to eighteen days, and wide for the back, seven to fifty days irrespective of type of treatment. All other burns show a range of healing of six to twenty-four days with either ointment or triple dye treatment, but a wider range of sixteen to ninety days with tannic acid-silver nitrate.

5. Second degree burns from scalds take as long to heal as those from flame burns. Scalds, however, have caused much wider areas to be involved in second degree burns without any parts of the burn being of third degree depth than have been seen in this series to result from flame burns.

INFECTION IN THIRD DEGREE BURNS

It is widely known that bacteriologic asepsis cannot be maintained for any length of time in third degree burns no matter what treatment is used. This infection is frequently very serious. Even under the most meticulous aseptic conditions staphylococcal infections are nearly universal and streptococcal and colon bacillus infections numerous.[16] In general, cultures taken from the infected surface of a burn show mixed infections. This is true of the cases in this series.

Infection occurs in or under the dead sloughing skin or eschar and always permeates or extends under it in time. For this reason it is important to consider the surface area exposed to toxic absorption. Table III shows the extent of third degree burns in the cases studied in this series.

All these patients received sulfadiazine beginning at 12 to 36 hours and continuing for fairly protracted periods of time. Very little important infection occurred in the 57 cases with nine per cent of area or less of third degree burns. Two children contracted a scarlet fever rash three days after the burn, probably not related to the treatment. Seventeen others had fevers of over 101°F. at some time after the first week. But in all these cases the fever lasted only a few days. None of these patients died.

The aseptic precautions taken on these cases were not as strict as might be desired. But certain essentials were rigidly carried out. If dressings were used they were large occlusive dressings infrequently changed. Attendants were masked and the careful aseptic technic was used when dressings were changed. The relative freedom from severe infection in these cases confirms the findings of Lyons,[16] that if pathogenic bacteria are present on the original surface of the burn they will die out rapidly under innocuous dressings and rest. Therefore, efforts should not be as much directed toward

TABLE III

STUDY OF 150 BURNS

AREAS INVOLVED IN CASES WITH MIXED SECOND DEGREE AND THIRD DEGREE BURNS

Total Area Burned % of Surface Area	Third Degree Burn % of Surface Area	Cases from C. G.	Other	Total
	0–1.5%	12	13	25
	2.0–6%	8	11	19
0–9%	Total	20	24	44
	0–2.5%	2	0	2
	3–6%	2	5	7
	7–9%	2	1	3
	10–16%	1	3	4
10–24%	Total	7	9	16
	5–9%	1	0	1
	10–19%	2	2	4
	20–24%	4	1	5
	25–35%	0	1	1
25–49%	Total	7	4	11
	45–49%	1	1	2
	55%	0	1	1
	No Estimate	0	1	1
50% plus	Total	1	3	4
	Grand Total	35	40	75

killing bacteria necessarily present as to preventing the addition of new pathogenic strains at later dates.[17] Attention to dust was not possible in this series.

The 18 patients with ten per cent area or more of third degree burn all had important infections, with fever for some time except for the patient mentioned above who died in shock at 22 hours after admission and the patient that died in five days with thrombocytopenic purpura, anemia, edema, azotemia, and anuria. The infections occurred irrespective of surface treatment employed and in spite of adequate sulfadiazine treatment.

The bacteria cultured from these cases with large area burns were no different from those cultured from the smaller ones. The larger the area the greater the constitutional reaction and the greater the loss of protein from the surface. All of these patients were definitely sick with fever, high leukocyte counts, loss of appetite, and all the other symptoms of acute infections. However, in no case was there any spreading infection from the edge of the burn into or under the adjacent skin or elsewhere.

NUTRITION IN SEVERE BURNS

All the patients with ten per cent of surface area, or more, involved in third degree burns became serious nutritional problems because of the losses of nitrogen in the urine and from the surface, and because of the increased nutritional requirements resulting from infection with fever.[18] All patients were started on high protein, high vitamin diets designed to give them double the normal protein intake and five times the normal vitamin

intake. This diet contained 140 Gm. of protein. Vitamin supplements were given to secure the following intakes: A, 25,000 units, D, 2000 units, thiamin, 10 mg., riboflavin, 15 mg., nicotinic acid, 200 mg., and asorbic acid, 300 mg. This took care quite adequately of all the cases with second degree burns or of third degree burns up to nine per cent. Much higher intakes of protein have been demonstrated to be needed by the cases with larger area burns.[18, 19, 20]

In addition, the amount of nitrogen losses and requirements are definitely proportional to the area of third degree burn. This is contrary to the findings of Cope,[21] and his associates. Presentation of data and further discussion of this important subject will be made in another communication.[18]

ANEMIA IN SEVERE BURNS

Ham,[22] and his associates, have shown that there was an early hemolysis with hemoglobinuria in some of the cases in this series. Later, a severe and persistent anemia developed. This latter finding has been reported by most authors working in this field for many years. In this series this anemia was combatted with iron and with frequent whole blood transfusions. It was very persistent in some cases and 500 to 1000 cc. of blood were given weekly for long periods of time.[23]

RESULTS OF TREATMENT OF THE 16 MOST SEVERE BURNS

Table IV shows the 16 most severe cases divided according to area involved, method of treatment, and result. In a few of these cases, minor areas were treated with experimental treatments. Such cases are classed according to the treatment of the major part of the burn. Also, if vaseline was used on hands or face and an eschar on all other areas, the case is classed according to treatment of the major area.

Table IV shows a very striking relation between the size of a third degree burn and the survival of the patient. Only three out of 11 patients with 20 per cent, or more, of the surface area destroyed by a third degree burn survived while none of the five patients with ten or 15 per cent of body area so destroyed died. This indicates that there is a critical area of third degree burn at about 20 per cent, beyond which the efforts employed in this series have not been able to save the patient. No conclusive evidence of the superiority of one type of treatment over either of the others can be derived from statistical analysis of the data.

The deaths were all preceded by great loss of weight and strength in spite of dietary measures, transfusions and other supportive treatment. The deaths were all relatively late, occurring on the following days after injury; 16, 25, 28, 32, 39, 80, and 157. In all studies of burns treated prior to the advent of plasma, these patients would probably have died of shock or "toxemia" at a much earlier time.

HEALING OF THIRD DEGREE BURNS

In a study of the efficiency of primary surface applications to third degree burns the true end-result, that of complete surface healing, cannot

TABLE IV

STUDY OF 150 BURNS

MORTALITY AFTER THE SECOND WEEK BY AREAS AND BY PRIMARY TREATMENT OF THIRD DEGREE BURNS

Per cent Area of Third Degree	Ointment		Tannic Acid-Silver Nitrate		Triple Dye		Total	
	Lived	Died	Lived	Died	Lived	Died	Lived	Died
10	1	0	1	0	0	0	2	0
15	1	0	0	0	2	0	3	0
20	1	0	0	5	1	0	2	5
35	0	1	0	0	0	0	0	1
45	0	0	0	1	1	0	1	1
65	0	0	0	0	0	1	0	1
Total	3	1	1	6	4	1	8	8

be used. Too many totally extraneous factors such as the technical success of grafting, the number of grafting operations; the severity of infection; the presence of anemia; and the state of nutrition are some of these factors. Two possible end-points, neither of which is ideal, may be used as rough guides to the efficiency of any application to such a burn. The first is the time of disappearance of gross slough, which is not a sharp end point and somewhat subject to "subjective" errors. The second criterion that may be used is not subjective (from the standpoint of statistical analysis), and that is the actual time of performing the first graft. As a test of a certain stage of healing this is far from perfect because any given patient may be operated upon too soon and, therefore, fail and another may be done later than necessary due to reasons that have nothing to do with the actual healing process. The time of the first successful graft would be a very poor test because the failure of a graft may be the result of technical errors and not due to any factor of unreadiness in the wound. During the earlier months of study it was thought that grafts could only be successful if all slough was removed, there was no fever, and no anemia, and no clinical infection. Later it was found that grafts could be successful even when put on areas of granulation that were surrounded by gross slough, provided the nutritional status of the patient was good, anemia was not present, and clinical infection not too active (Fig. 2 A-D).

In addition to these reservations there is another even greater obstacle to the study of the results of any original application to these cases. This is due to the impossibility of keeping the secondary treatment of the cases absolutely uniform. In general, secondary treatments consisted of applications either of vaseline or boric acid ointment or of saline or weak Dakin's solution or by various combinations of these. The time of starting and the frequency of the secondary dressings varied to a large extent according to such uncontrollable factors as the reactions of the patient, the area of the burn, whether general anesthesia was necessary for dressing or not. If an attempt is made to classify the cases according to the sequence and frequency of the various dressings the number in each class becomes so small as to have no statistical value. For this reason no attempt is made

to correlate the effects the various secondary treatments may have on the time of healing. Because of these same factors Tables V and VI are presented as indicating, in only a very limited way, any effects of the primary surface treatment.

TABLE V

STUDY OF 150 BURNS

HEALING OF THIRD DEGREE BURNS, GRAFTED CASES

	F. G. S.—Days			T. F. G.—Days			No. of
	Min.	Max.	Av.	Min.	Max.	Av.	Cases
Small ointment	16	28	24	21	72	33	11
Large ointment	21	60	32	21	120	39	8
All ointment	16	60	27	21	120	36	19
Small tannic-silver	34	36	35	39	44	42	2
Large tannic-silver	36	55	41	43	66	51	4
All tannic-silver	34	55	39	39	66	48	6
Small triple dye	24	38	33	35	62	44	6
Large triple dye	18	60	39	27	119	54	6
All triple dye	18	60	36	27	119	49	12
All small	16	38	28	21	72	38	19
All large	18	60	36	21	120	47	18
Total	16	60	32	21	120	42	37

F. G. S. equals free of gross slough.
T. F. G. equals time of first skin graft.
"Small" burns are 3% or less of surface area.
"Large" burns are 4% or more of surface area.

TABLE VI

STUDY OF 150 BURNS

HEALING OF THIRD DEGREE BURNS WITHOUT GRAFTING

	F. G. S.*—Days			No. of	Healed—Days			No. of
	Min.	Max.	Av.	Cases	Min.	Max.	Av.	Cases
Vas	14	30	20	14	28	72	44	8
T. S.	28	45	35	4	—	—	40	1
T. D.	25	30	28	2	38	64	51	2

*F. G. S. equals free of gross slough.

Table V suggests that areas treated with vaseline became free of slough earlier and shows that they were grafted earlier than areas treated by other methods. It also shows that cases with small areas were free of slough and were grafted earlier than larger cases. This is contrary to the findings of Cannon[24] in regard to the separation of slough. He had to delay the grafting of his most severe case until the 77th day because of various complications. A similar delay for similar reasons occurred in several of the cases in this series that had comparable or larger areas of third degree burn.

Thiersch grafts were applied in all but two instances. In these exceptions Reverdin grafts were employed. The condition of the patient with 45 per cent of surface area involved would not have permitted a Thiersch operation even if enough suitable donor sites could have been found. Sixty-two per cent of the first Thiersch grafts on all cases grafted were fully successful; 14 per cent partially successful; and 24 per cent failed. All areas treated without grafting were necessarily small and usually consisted of

multiple small areas. The smaller number of cases recorded in Table VI, under healing time, is due to the fact that information concerning some cases was secured by letter or telephone and not by direct observation, and such information has not been used. The table shows that in them there was a more marked difference in favor of vaseline so far as the time required for the slough to disappear is concerned, but essentially no difference in the time of final healing. This is to be expected as the latter is dependent on the exact sizes and shapes of areas and possibly on the efficiency of secondary treatment rather than on the original treatment.

Further analysis of the available data permits the following statements to be made:

1. If Tables V and VI were separated into "Cocoanut Grove" cases and other cases, no difference in results would be found.

2. Deep burns became free of slough after a longer interval than burns that barely removed all epithelial elements. This was particularly true if fascia or tendons were involved, as was true in some of the patients with burned hands.

3. Location of the burned area was not as important as in second degree burns although, again, the thick skin of the back was usually slow to separate even when the underlying fascia was not involved.

4. Third degree burns from scalds, although less common, reacted in no way differently from third degree burns of the same size and depth that were caused by other forms of thermal trauma.

SUMMARY AND CONCLUSIONS

1. One hundred and fifty cases of burns have been studied from the point of view of comparing results following surface applications of ointment gauze dressings, tannic acid-silver nitrate, and triple dye.

2. There were two slight clinical infections in 75 patients that had second degree burns only, and none of the 75 patients died.

3. Edema of the face disappeared very rapidly without any application of pressure.

4. Skin healing of second degree burns of all areas except the back, took place a few days earlier if ointment or triple dye were used than if tannic acid was used. Skin healing of second degree burns of the back took place a few days earlier if vaselined gauze or boric acid ointment were used for treatment than if either tannic acid-silver nitrate, or triple dye were used.

5. Skin healing of second degree burns of the face was faster and of the back slower than of all other parts of the body.

6. Fifty-seven patients had mixed second and third degree burns with nine per cent, or less of body area involved in third degree burn. There were 19 instances of clinical infection in these cases, but none were serious. None of these patients died.

7. Eighteen patients with more than ten per cent of surface area involved by a third degree burn either died or were seriously ill before recovery.

8. One patient died from shock at 22 hours following inadequate plasma administration.

9. One patient died at five days with thrombocytopenic purpura, anemia, edema, azotemia, and anuria as complications.

10. The remaining 16 patients demonstrate that patients with 20 per cent, or more, of surface area involved in a third degree burn have a very critical burn. All five patients with 10 or 15 per cent of third degree burns survived, while only three out of eleven with 20 per cent, or larger, areas survived.

11. All the patients who died and many of those who lived with third degree burns of ten per cent area, or more, showed infection, severe loss of weight, and critical metabolic disturbances including azotemia, hypoproteinemia, anemia, and abnormally high losses of nitrogen.

12. The statistics suggest, but do not prove, that vaselined gauze and triple dye treatment were safer for large third degree burns than treatment with tannic acid-silver nitrate.

13. Small third degree burns became free of slough and were grafted earlier than large ones.

14. Areas treated with vaselined gauze became free of slough and were grafted earlier than areas treated with the other two methods.

The authors acknowledge with deep gratitude the enormous labors of the hospital staff, in all grades, and in all departments, and of several other agencies and individuals too numerous to name, without whose help the study of and care of these patients, particularly those from the Cocoanut Grove disaster, could not have been carried out.

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GUNSHOT WOUNDS OF THE ABDOMEN

A SURVEY OF 238 CASES

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PRIOR TO WORLD WAR I conservative treatment was generally advised for gunshot wounds of the abdomen received during battle. In the American Civil War there were 3,690 such cases, with a mortality of 90 per cent.[1] In the Spanish-American War there were 44 cases reported. Four were operated upon, and all four died. Of the remaining 40 that were treated conservatively, 25 died, a mortality of 62.5 per cent.[1] During the Boer War (1900) and the Russo-Japanese War (1904-1905) these patients were treated by starvation and large doses of morphine.[2] Because of such war reports, the military surgeons in the early days of World War I were of the opinion that practically all cases recovered were not operated upon. The reports from civil life pointed to a more favorable result with early operation. Grant,[3] in 1899, collected 253 civilian operated cases of gunshot wounds of the abdomen, with a mortality of 52 per cent.

Early in World War I, Leriche[4] reported that the mortality with conservative treatment was over 80 per cent, and advised early operation. In 1916, Wallace[5] reported a study of 1,200 cases of gunshot wounds of the abdomen among the British Expeditionary Forces. In this large group the mortality of the operative cases was 53.9 per cent, which was not strikingly less than the total mortality of 60.2 per cent, including the nonoperative cases. In 1917, Lockwood and Kennedy[6] reported 500 cases seen in an advanced casualty station. There were 356 operative cases, with a mortality of 51.7 per cent.

In 1924, Condict[7] reported nine deaths in 20 cases of gunshot wounds of the abdomen seen at the Gouveneur Hospital, New York. In 1931, Billings and Walking[8] reported 114 cases from Philadelphia, with an operative mortality of 48.2 per cent. Prey and Foster[9] reported a 68 per cent in 22 cases. McGowan[10] analysed 164 cases of penetrating wounds of the abdomen, of which 64 were gunshot wounds, with a mortality of 59.3 per cent. Oberhelman and Le Count[11] reviewed 343 cases from the Cook County Hospital, with a mortality of 61.4 per cent in the operative cases. In 1938, Taylor[12] reported 101 cases of gunshot wounds of the abdomen which included 11 that had been shot with shotguns. There was a mortality of 53.4 per cent for the operative cases of the entire group. In an analysis of 35 personal cases Storck[13] was able to show a mortality of 40 per cent. In 1941, Rippy[14] reviewed 369 cases that were seen in a 17-year period. Three hundred and thirty-seven of the patients were operated upon, with a mortality

of 60.5 per cent. The mortality of 29 of these cases treated in 1940 was 41.3 per cent. He also presented 36 cases of shotgun wounds of the abdomen, with a mortality of 80.5 per cent. More recently, Hamilton and Duncan[15] reviewed 336 cases of penetrating wounds of the abdomen. The total mortality for 190 gunshot wounds was 51 per cent; the operative mortality for 182 cases was 48.9 per cent.

This study is based on 238 patients who were admitted from January 1, 1937, to January 1, 1943, to the Surgical Service of the Emory University division of Grady Hospital, with the provisional diagnosis of gunshot wound of the abdomen. All of the patients were Negroes. Those who died in the emergency clinic before admission to the wards are not included. With this exception, the cases were consecutive. Of the 238 patients included in this series, 29 were shotgun wounds and 209 were produced by rifle or pistol.

Shotgun Wounds.—Of the 29 patients wounded with shotguns, two died before any operative procedure could be carried out. Nine patients were not operated upon because it was thought that very few, if any, of the pellets had entered the abdominal cavity and that the small perforations, should there be any, would seal spontaneously. In this group there was one death from pelvic abscess and peritonitis. This death occurred three weeks after admission. One of the unoperated patients required a transfusion after passing fresh blood in the stools. Six of the operative cases required resection of involved intestine; one of these survived, and in this instance an exteriorization and delayed anastomosis was done. Those requiring resection were shot at close range with resulting extensive destruction of the abdominal wall, and often there was serious damage to the liver, kidney, pancreas and large blood vessels. The mortality for the operated group was 55.5 per cent, and the total mortality for the entire group, including the unoperated cases and those that died immediately after admission, was 44.8 per cent (Table I).

TABLE I

SUMMATION OF 29 CASES OF SHOTGUN WOUNDS

	Died Immediately	Operated		Not Operated	
		Died	Improved	Died	Improved
1937			1		1
1938		2			2
1939	1	1			
1940		2	2		5
1941	1	4	2		
1942		1	3	1	
	2	10	8	1	8

Pistol and Rifle Wounds.—In the group of 209 patients who were shot with pistols or rifles, 15 died before any operative procedure could be carried out. These patients were admitted in severe shock and did not respond to intravenous fluids or transfusions. One patient refused operation and left the hospital against advice; it was thought that his only injury was to the liver. His death was not subsequently recorded. Thirteen patients

were not operated upon because it was thought that the bullet did not enter the peritoneal cavity; one of these died, and autopsy revealed a large abscess in the right paracolic space. One patient was admitted to the hospital with an abscess extending above the umbilicus and pointing in the pelvis, three weeks after having received a bullet wound in the right lower quadrant. She improved after drainage of the abscess. Of the 181 patients in this group who were operated upon, 84 died and 97 were discharged improved, making a mortality rate in the operative group of 46.4 per cent. The total mortality, including those that died soon after admission, was 47.8 per cent (Table II).

TABLE II

SUMMATION OF 209 CASES OF PISTOL AND RIFLE WOUNDS

	Died Immediately	Operated		Not Operated	
		Died	Improved	Died	Improved
1937	4	21	18		3
1938	5	15	17		3
1939	1	11	9		
1940	2	15	18		3
1941	1	16	18	1	1
1942	2	6	17		2
	15	84	97	1	12

Injuries Found at Operation.—In the group of 181 patients wounded with pistols and rifles who had exploratory celiotomies, a combination of large and small intestinal wounds was found most frequently. Injury to the small intestine alone was next frequent and injury to the large intestine alone was third in order of frequency. The injuries and results are recorded in Table III.

Cause of Death.—Seventeen of the 238 patients died immediately after admission, and four died on the operating table. Shock and hemorrhage were striking findings. Forty-seven of the 94 postoperative deaths (50 per cent) occurred within 48 hours. These deaths are arbitrarily classified as due to shock and hemorrhage, pneumonia and peritonitis, or combinations of these. Mason,[17] and Loria[18] have emphasized the influence of hemorrhage on the mortality. Severe blood loss seems to predispose to the development of pneumonia and peritonitis, hence there is much confusion of these factors as the actual cause of death in the early postoperative period. Twenty deaths occurred between the second and seventh postoperative days and, with one exception, all were due to pneumonia or peritonitis. The exception was a case with evisceration on the fifth and death on the sixth postoperative day. The late complications and their results are shown in Table IV.

Chemotherapy.—Thirty-three of the entire operative group of 199 patients were given sulfanilamide. Fourteen received the drug subcutaneously and 19 received it both subcutaneously and intraperitoneally; the number of deaths was six and five, respectively, making a mortality of 33 per cent. The drug seemed to be of considerable value in controlling the peritonitis. The average amount used intra-abdominally was 5 Gm.

TABLE III

TABULATION OF LOCALIZATION AND RESULTS ON PISTOL AND RIFLE WOUNDS OPERATED UPON

	No. of Cases	Died	Lived
Stomach	8	4	4
Stomach and small intestine	3	2	1
Stomach and liver	1	1	0
Stomach and kidney	1	1	0
Stomach and pancreas	2	1	1
Stomach and colon	4	3	1
Stomach, pancreas and kidney	1	1	0
Stomach, kidney and spleen	1	1	0
Stomach, colon and small intestine	1	1	0
Stomach and chest	2	2	0
Liver	16	3	13
Liver and kidney	6	4	2
Liver and chest	1	1	0
Liver and colon	1	0	1
Liver, stomach, pancreas and kidney	1	1	0
Small intestine	37	14	23
Small intestine and colon	32	15	17
Small intestine and bladder	2	1	1
Small intestine, bladder and rectum	3	1	2
Small intestine and head	1	1	0
Duodenum and colon	1	1	0
Duodenum and liver	2	2	0
Large intestine	17	8	9
Colon and appendix	1	1	0
Colon and chest	1	1	0
Bladder	3	0	3
Gallbladder, liver and stomach	2	0	2
Kidney	3	0	3
Kidney and spleen	2	1	1
Kidney, colon and small intestine	4	3	1
Kidney and chest	1	1	0
Spleen, large and small intestine	3	2	1
Blood vessels:			
Aorta and vena cava	1	1	0
Aorta and small intestine	1	1	0
Vena cava and small intestine and colon	1	1	0
Portal vein	1	1	0
Common iliac	1	1	0
No perforations found	7	1	6
No peritoneal perforation	5	0	5
	181	84	97

Diagnosis.—In most instances, the diagnosis offers little difficulty. It is desirable to ascertain the time interval between the injury and hospitalization and, if possible, the direction of line of fire. As emphasized by Meyer and Shapiro,[19] the back and sides, as well as the front of the abdomen, should be inspected and palpated carefully. When there is no wound of exit, frequently the bullet may be felt immediately beneath the skin at some distance from the point of entrance. Eisberg[20] has called attention to the need for careful study of the point of entrance in order to determine the direction of the bullet. When the bullet enters the skin obliquely, an area of abrasion appears on the proximal side of the wound and an area of undermining in the subcutaneous tissue. Muscle rigidity may be absent or as pronounced as that found with ruptured viscus. Palpation of the umbilicus or palpation of the pelvic peritoneum by rectum

TABLE IV

LATE POSTOPERATIVE COMPLICATIONS OTHER THAN PNEUMONIA AND PERITONITIS

	No. of Cases	Deaths
Postoperative obstruction requiring operative relief	5	2
Pelvic abscess	8	5
Empyema	3	3
Liver abscess	2	1
Subdiaphragmatic abscess	1	0
Pylephlebitis	1	1
Postoperative evisceration	5	1
Granuloma of lung	1	1
Arteriovenous fistula (femoral), postoperative gangrene of leg	1	1
	27	15

will reveal cases with minimum peritoneal irritations. Occasionally, when the internal injury is confined to the chest and associated with a hemothorax, there may be rigidity and tenderness of the upper abdomen. The presence or absence of peristalsis cannot be relied upon; it may be present when there is either blood or small amounts of solid feces present in the abdominal cavity. Many of the cases seen early have peristalsis.

Immediately upon admission to the hospital a urine specimen should be collected and examined for blood. If no urine or only a few drops of blood are found on catheterization, it is probable that there has been a perforation of the bladder. Roentgenologic examinations are helpful in many instances. They may indicate the position and probable course of the bullet or may reveal the presence of free air in the peritoneal cavity, and thus influence the location of the incision. Some patients have practically no abdominal findings except the wound of entrance; therefore, it is best to explore the wound of entrance to determine the depth and direction of penetration or to explore the abdominal cavity if it is at all possible that the bullet had entered it. To await signs of peritoneal irritation is not justifiable. Peritoneoscopic examination has been advocated by Hamilton[21] in questionable cases of penetration of the peritoneum.

PREOPERATIVE OPERATION

Patients in shock are immediately placed in Trendelenburg position. Fluids are administered intravenously in all cases. Many of the patients will require blood or plasma. When urgency demands, Group "o" blood may be given without cross-matching. Morphine sulphate is administered immediately unless the patient is in an alcoholic stupor. Warm blankets and hot water bottles are placed about the patient. A tube is inserted into the stomach through the nose, the gastric contents are aspirated, and the tube is left in place. If sufficient time elapses in the preoperative period, 500 cc. of 0.8 per cent (4 Gm.) sulfanilamide, is given subcutaneously as the initial dose. Mixed antianaerobic serum and 1500 units of antitetanic serum is administered prophylactically to all patients. Attempts are made to move the patients to the operating room quickly and in the best possible condition. Supportive measures can be continued during the operation.

Anesthesia.—Although spinal anesthesia has been advocated for selected

cases, its safety cannot always be predicted. Nitrous oxide-oxygen induction followed by ether is safest. Some method for aspirating the pharynx and trachea should be available.

OPERATIVE PROCEDURE

Wounds of entrance and exit are first excised, treated with sulfanilamide crystals, and packed.

Muscle-splitting rectus incisions have been used for all explorations. In most instances this is placed on the right side and gives ample exposure to explore the entire contents of the abdominal cavity. Occasionally, the left rectus incision, or a transverse incision in the flank, will offer better exposure of the area of greatest damage.

Immediately upon opening the abdomen the contents of the peritoneal cavity are aspirated. Vigorous bleeding, if present, is controlled. Usually, bleeding from the liver can be temporarily controlled with moist, hot packs, and bleeding from large mesenteric vessels with digital compression of the root of the mesentery, until clamps can be placed on the open vessels. Hemorrhage from wounds of the larger vessels is controlled with digital pressure until the site of bleeding is exposed and sutured. Autotransfusions, as suggested by Hamilton and Duncan,[15] may be employed under desperate circumstances.

Usually, the cecum is examined first; the small intestine is then inspected from the ileocecal junction to the ligament of Treitz, using warm, moist packs to handle the intestine. Any perforations are repaired as they are found. Should a resection be necessary, clamps are placed on the open ends as a landmark, while the remainder of the small intestine is examined; thus avoiding the possibility of performing two anastomoses that could readily be converted into a single one without the loss of too large a segment.

The large intestine is explored next. Solid feces is removed with dry gauze sponges. The stomach and retroperitoneal structures are then carefully examined. Moderately-sized retroperitoneal hematomata are left undisturbed unless they involve the kidneys, pancreas or duodenum. Longer incisions and evisceration, as advocated by McGowan,[10] and Connors,[22] should be used if areas of injury cannot be exposed adequately. Minor lacerations of the kidney or spleen can usually be sutured; otherwise these organs should be removed. Most wounds of the liver are not bleeding at the time of exploration, but if active bleeding is present sutures on a large, half-round, blunt needle can be used. In some instances it is necessary to use a gauze pack which is brought out through the incision or a stab wound. Perforations of the diaphragm (on the left) should always be closed to avoid the possibility of herniation.

All perforations in the intestines are freed of protruding mucosa and closed transversely with a running suture of fine chromic catgut, which includes all layers. This, in turn, is inverted with interrupted sutures of fine silk. Silk has been used on many occasions for the initial line of sutures and no

apparent difficulty has been encountered. However, silk should never be used in bladder mucosa since it may initiate calculus formation.

After completing the exploration and repair of injuries, the peritoneal cavity is again aspirated. No attempt should be made to irrigate the peritoneal cavity. Peritoneal drains are not indicated. Four to 6 Gm. of sulfanilamide crystals are dusted into the abdomen. At the present time this seems to be the drug of choice for these cases.[23, 24] The peritoneum is closed with catgut. The remainder of the wound, including all layers except the peritoneum, is closed with through-and-through sutures of silver wire or silkworm gut. About 1 Gm. of sulfanilamide is placed in the incision.

POSTOPERATIVE TREATMENT

The patients are placed in Fowler's position after reaction, unless shock is evident. Constant suction with an indwelling tube is applied to the stomach and 4,000 to 5,000 cc. of fluids is administered daily. Sulfanilamide is given subcutaneously, using 150 cc. of 0.8 per cent solution (1.2 Gm.) every six hours. Frequent blood sulfanilamide determinations should be made. The appearance of jaundice and anemia are indications for discontinuation of the drug. In the absence of toxic effects, administration is continued subcutaneously until sulfadiazine can be taken by mouth. This usually takes four to five days in uncomplicated cases. When peristalsis is normal, the abdomen soft, and flatus is being passed by rectum, gastric suction can be discontinued and water given by mouth. During the immediate postoperative period oxygen with 5 per cent carbon dioxide is administered every 4 hours to prevent pulmonary atelectosis. Obstruction and paralytic ileus occurring in the early postoperative period respond well to the use of the Miller-Abbott tube. Feeding is begun on the sixth or seventh day. Wound infection, pelvic abscess and subphrenic suppuration should be carefully watched for.

Discussion.—The mortality rate in gunshot wounds of the abdomen has remained high (and will probably continue to remain high) because there is always a large percentage of deaths by virtue of extensive damage to the abdominal viscera and large blood vessels. The factors that determine mortality fall into two groups: (1) Those that cannot be influenced by the surgeon's skill and management; and (2) those that can be minimized by greater efficiency in treatment. The severity of the wound, the time required to reach the hospital where adequate therapy can be instituted, and the physical status of the patient prior to receiving the injury are obviously uncontrollable factors. The type of anesthesia, the prompt but complete exploration, with repair of damage, the proper use of chemotherapy, and the postoperative management are all factors which are definitely controllable.

Many of the patients considered here were intoxicated and some were in an alcoholic stupor. Their state of nutrition was frequently poor; syphilis and cardiovascular diseases were common. The severity of hemorrhage and shock was controllable to some extent by the prompt administration of

plasma or whole blood, thus allowing the patients to be brought to operation more quickly, and increasing the chances of survival.

SUMMARY

1. A statistical review of 238 cases of gunshot wounds of the abdomen is presented.

2. The general plan of treatment is discussed.

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PRINCIPLES UNDERLYING THE OPERATIVE APPROACH TO THE TREATMENT OF MYOCARDIAL ISCHEMIA*

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I SHOULD LIKE TO RECORD THE RESULTS obtained by my associates and myself on the subject of revascularization of the heart. This work represents the results of several thousand experimental operations upon the heart carried out during the past ten years. I should also like to comment upon the nature of coronary artery disease in reference to the operative approach for its relief. Thirty patients with sclerosis of the coronary arteries were operated upon between the years 1935 and 1938. This small group of patients were regarded as a study group. The clinical results in the patients who survived the operation were satisfactory, and seven additional patients were operated upon before the present war interrupted further application of this work. The results in the patients will be recorded by Dr. Harold Feil.

It is clear to me that the principles underlying the operative approach to this subject must be based upon experiment. The underlying concepts for this approach cannot be plucked out of thin air, no matter how enterprising the surgeon may be. I do not believe it is possible to contribute to these principles in the early stages of this work by operating upon patients. The operation is not based upon extirpation. The surgeon cannot take out the diseased arteries nor can he remove an infarct. The principles underlying the operation must be brought to light by carefully controlled experiment before he justifiably can apply the operation to patients.

One concept which has come out of this experimental background concerns the nature of coronary artery disease. It can be compared with epilepsy. As sclerosis of the blood vessels develops a zone of anoxemia appears. In the heart, as in the brain, an irritable focus or "trigger" appears which can "fire" and destroy the normal physiology. A focus in the brain produces a convulsion; a focus in the heart destroys the coordinated rhythmic contraction and relaxation of muscle fibers and produces ventricular fibrillation. Some fibers are relaxed while others are contracted. The heart cannot expel blood and the patient dies. I need scarcely say that the man who has a trigger developing in the heart usually does not have a failing heart. When it "fires" it is sudden, often unexpected and always final and irreversible.

Another concept which has come out of the experimental work is that of a blood-bath to the trigger zone. By this term is meant an amount of oxygenated blood which (1) will reduce the irritability of the zone

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and prevent it from "firing"; and (2) will preserve the viability of heart muscle and prevent it from degenerating into scar tissue.

The requirements for a blood-bath cannot be given in cubic centimeters of flow per minute but can be indicated by an illustrative experiment. A trigger can be readily produced by ligation of a number of small arteries leading to a zone of myocardium (Fig. 1). In this experiment one small artery after another is ligated and the myocardium supplied by these arteries becomes increasingly cyanotic. For purposes of quantitative illustration, I can say that the zone does not "fire" when five of these small arteries are ligated. The animal can recover from these ligations. However, if an

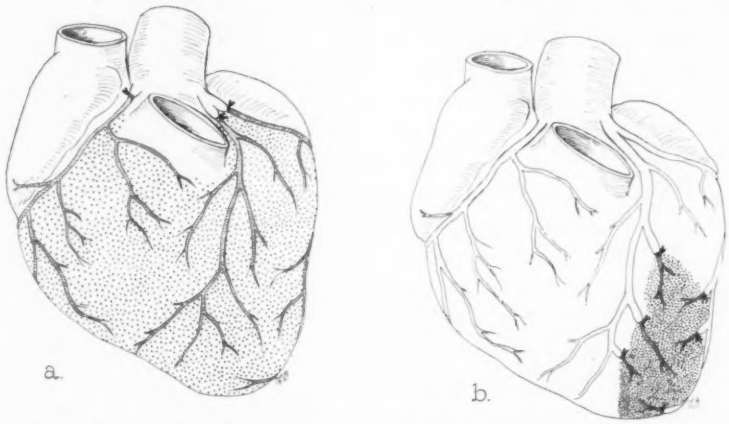


FIG. 1.—Two types of coronary artery occlusion.
A. Partial occlusion of three major arteries. This may be tolerated by the heart.
B. Complete occlusion of six arteries to a small area of the left ventricle. This produces a trigger which in turn produces ventricular fibrillation and death. A blood-bath to this area is prophylactic.

additional artery is ligated the trigger does "fire" and the animal is lost. This one additional channel, small as it is (but not insignificant), may be regarded as "the last straw." I think this experiment clearly indicates that a small amount of blood can be effective as a blood-bath. Repeated experiment has emphasized, over and over again, the significance of a small amount of blood delivered to that part of the myocardium where the blood supply is deficient. Those who are adversely critical of this research on coronary artery disease and the surgical approach to its treatment will please bear this point in mind. A small amount of blood can make the difference between recovery and death. Our experiments have shown that there are three methods of approach for the production of a blood-bath (Table I).

TABLE I

A Blood-Bath Can be Provided by Operative Methods:

1. By establishment of extracoronary communications. This can be done by grafting tissues upon the heart.
2. By establishment of intercoronary communications. This can be done in two ways:
   a. By inflammation on surface of heart produced by operative methods. Asbestos produced the most favorable response.
   b. By providing a time factor so that arterial occlusion becomes effective. This can be done by methods 1 and 2a of this outline.

Extracoronary Communications.—These are produced by grafting tissues upon the heart. The tissues available are numerous. I can mention pericardium, mediastinal fat, chest wall, lung, diaphragm, stomach, spleen and omentum. We used these various structures experimentally in our early work but the use of some of them is not practical. *My chief concern has not been whether pectoral muscle or omentum should be used but whether vascular communications can be demonstrated by any method and with any tissue.* It is up to the surgeon to show what he can produce in the way of communications and it requires more than a few experiments to make a satisfactory demonstration of these vascular communications. Figure 2 shows some specimens showing these communications. The coronary arteries have been injected with a mixture of barium sulfate and gelatin and the specimens have been cleared by the Spalteholtz method. The blood vessels can be readily seen extending from the coronary arteries out into the blood vessels in the grafts that were placed on the heart. There are communications between the heart and the grafts. They are large enough to be seen without magnification. Let us try to interpret these anastomoses in terms of whether they might be adequate to produce a blood-bath.

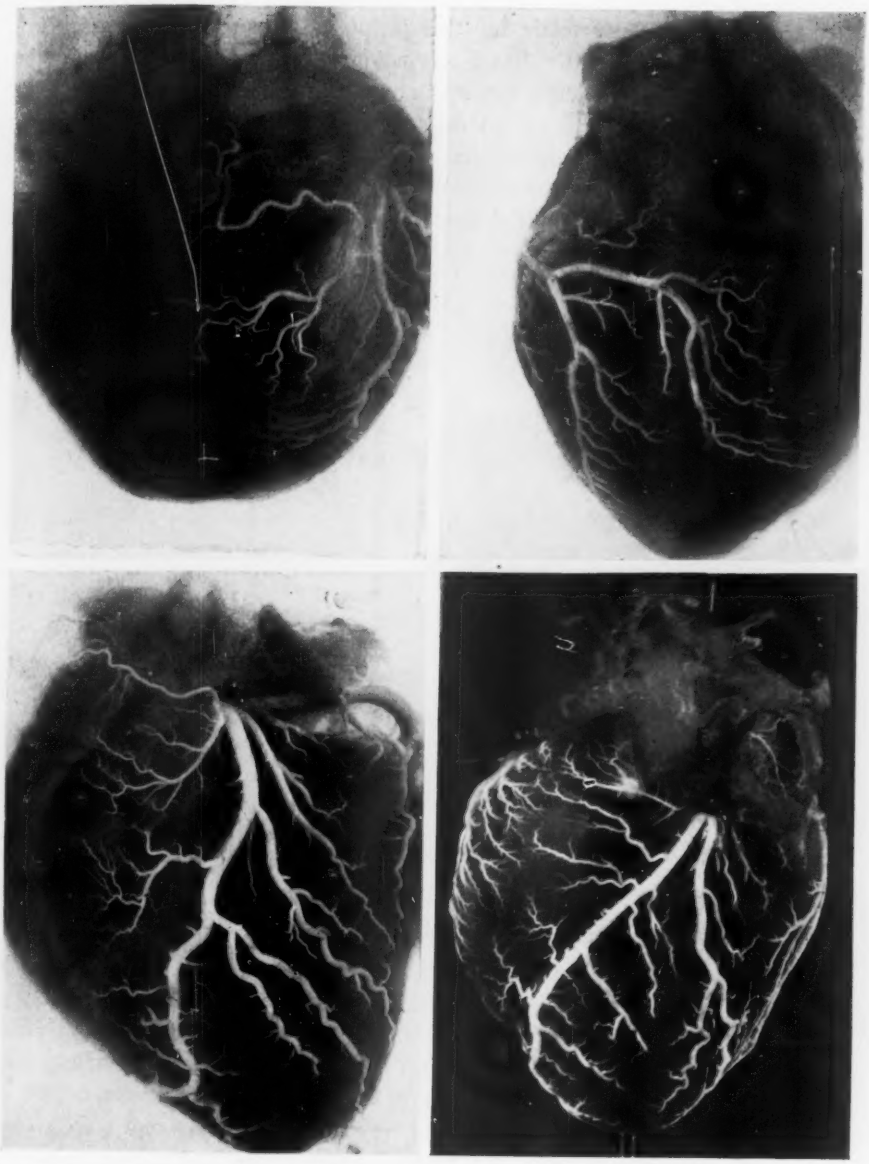
Intercoronary Communications. The coronary arteries are essentially end-arteries. If one coronary artery is injected with a mixture of barium sulfate and gelatin practically none of this mixture passes beyond the arterial bed of the injected artery (Fig. 3). If the descending ramus of the left coronary artery is ligated during life and then transected distal to the ligature it will be found that the blood emerging from the artery in a retrograde direction "can be measured only in drops not in cubic centimeters per minute." (Wigger's Text Book of Physiology). This small quantity of blood comes from intercoronary communications. Because of this anatomic arrangement we find that the heart is predisposed to the development of a trigger or an infarct when a major artery is occluded. Conversely, if some communications between coronary arteries are present then one of these arteries can be ligated without producing a trigger and without producing necrosis of muscle. With a full appreciation of the value of intercoronary communications, let us inquire into the methods by which they can be produced. Intercoronary communications can be produced in two ways: One is by the production of inflammation on the surface of the heart. The other is by coronary occlusion plus a factor of time.

A—INFLAMMATION ON THE HEART

It occurred to me early in our experimental work that a bed of granulation tissue on the heart would increase vascularity and distribute blood to every part of the heart. I used powdered beef bone to produce an inflammatory reaction, both experimentally and on patients. This was the first attempt to produce inflammation on the surface of the heart. We did not make any measurements of the amount of help this procedure afforded until

A

B



C

D

FIG. 3.—Normal hearts: Coronary arteries injected with mixture of barium sulfate and gelatin. The coronary arteries are practically end-arteries but a few intercommunications can be found in some specimens.

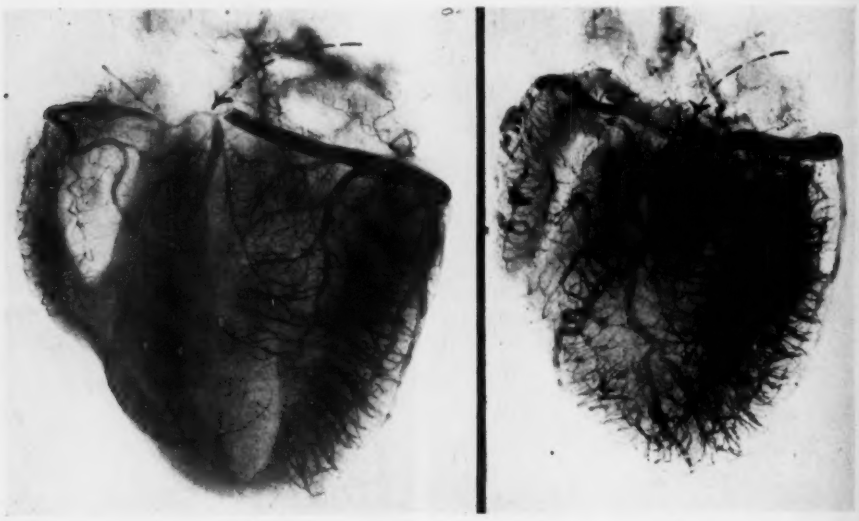
A. Left circumflex artery injected. Small amount of barium sulfate can be seen in descending ramus of left coronary artery.

B. Circumflex branch of left coronary artery injected.

C. Common left coronary artery injected.

D. Three coronary arteries injected.

Stanton, Schildt and myself[1] carried out such studies two years ago. We exposed the heart by operation and then abraded or scraped off the epicardium by special burs made for this purpose. The incision was closed. One to three weeks later the heart was again exposed at operation and the descending ramus of the left coronary artery was ligated at its origin. This experiment was performed on 50 dogs. Ligation of the artery alone was performed in another group of 50 dogs. The mortality in this control group was 70 per cent. The mortality in the group, in which the surface of the heart was abraded at the first operation and the descending ramus



A B

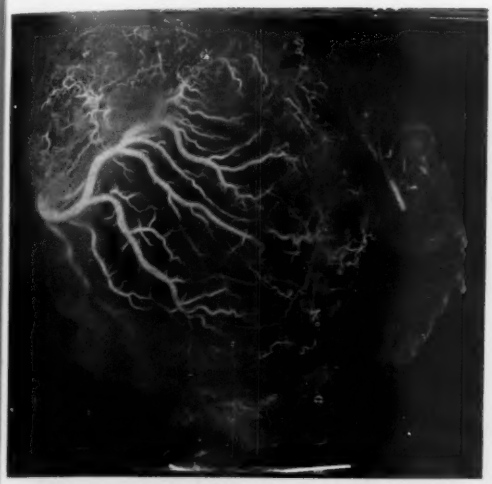
FIG. 4.—Circumflex branch of left coronary artery and the right coronary artery were injected with a mixture of barium sulfate and gelatin. The descending ramus of the left coronary artery is indicated by the arrow. Note the difference in the injection in these specimens.

A. A normal heart.

B. A heart, the surface of which was abraded at operation two weeks before killing the animal for injection. The degree of injection in the descending artery is an indication of the intercoronary communications present in these hearts. (A) Shows the greatest injection out of a group of ten normal hearts and (B) shows the greatest injection out of a group of ten abraded hearts.[1]

of the left coronary artery was ligated at its origin in the second operation, was 38 per cent. We could demonstrate intercoronary anastomoses in many of these abraded hearts (Fig. 4) and, indeed, in some of the specimens the infarct was small, or there was no infarct at all, after the artery had been ligated. The absence of an infarct in something that never occurs in a normal heart after ligation of this artery at its origin in one step. This is a simple experiment and I do not see where there can be any misinterpretation of results. Indeed, insofar as the reduction in mortality is concerned, we might note that each of the control group had one anesthesia and one operation while each of the other experiments had two anesthesias and two operations. The difference in mortality is definite and conclusive. One does not like to abrade the human heart because it produces extrasystoles and tachycardia.[2] Fortunately, it is not necessary to do this at operation because the application of inflammatory agents on the heart

2A



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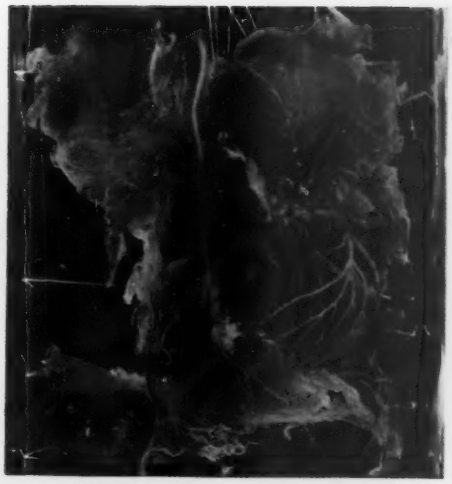

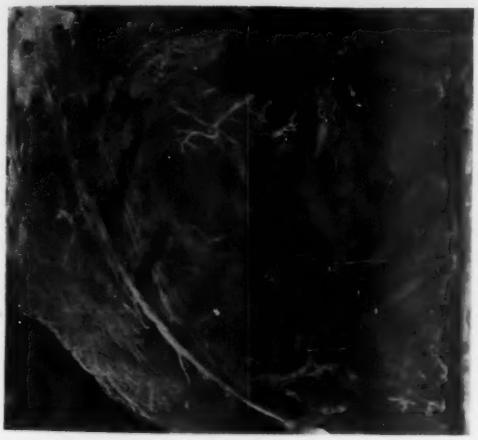

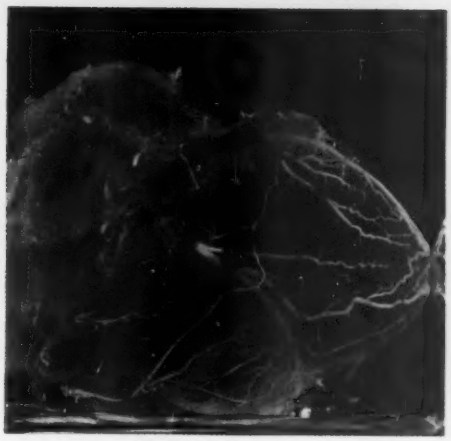

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FIG. 2.—A. Epicardium stripped off, asbestos applied, heart brought into contact with chest wall. Specimen five weeks later. Coronary arteries injected. Note extracoronary communications and internal mammary artery. These anastomoses developed without stimulus of coronary artery occlusion.

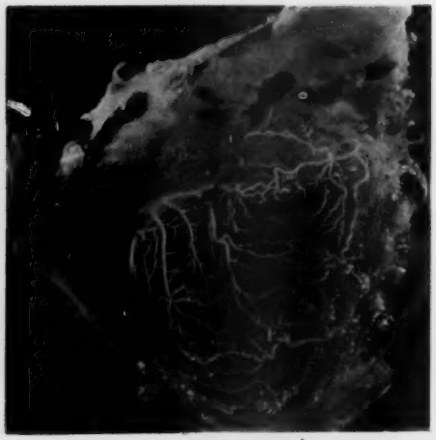
B. Substernal muscle with internal mammary arteries grafted on the heart. Arterial occlusion at subsequent operations. Specimen injected through coronary arteries. Note injection of internal mammary and other arteries of graft.

C. Heart abraded, brought into contact with chest wall, asbestos applied. 16 days later descending coronary artery occluded. Dog killed after three months. Right and circumflex coronary arteries injected. Descending artery filled as did also the internal mammary artery of the chest wall.

D. Epicardium abraded, asbestos applied, pericardium grafted onto heart. Later on, descending coronary artery and right coronary artery were completely occluded by repeated operations. Several months later, specimen removed and circumflex artery was injected. Note filling of right and descending ramus of left coronary artery. Also note actual communications between coronary arteries and arteries of the pericardium.

These colored reproductions are necessarily reduced in size. It is suggested that they be observed through a magnifying glass.

5A



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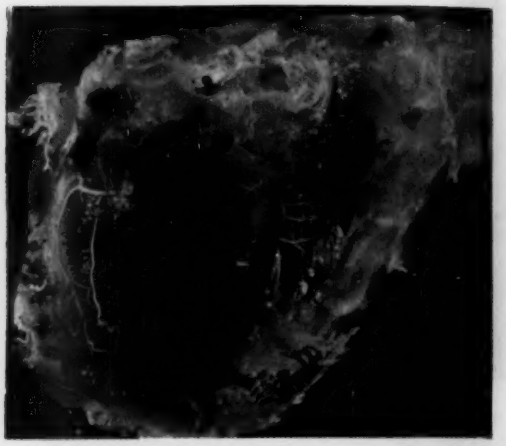

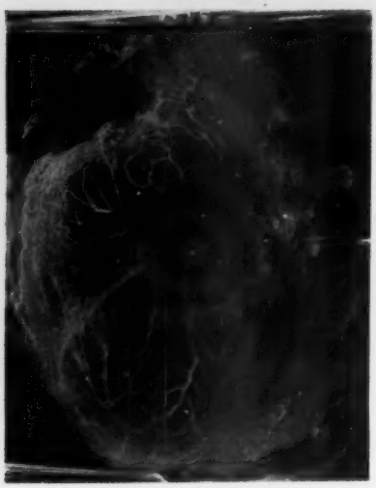

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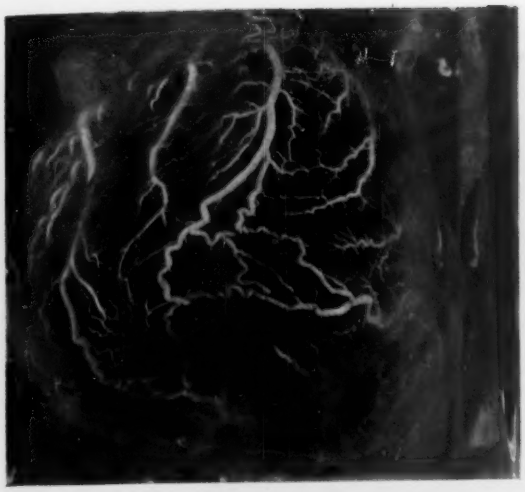
FIG. 5.—In these specimens the epicardium was abraded, asbestos was applied and grafts were placed. Coronary arteries partially occluded at subsequent operations. Note intercoronary and extracoronary communications. (C) Had a graft of omentum and shows many blood vessels.

6A



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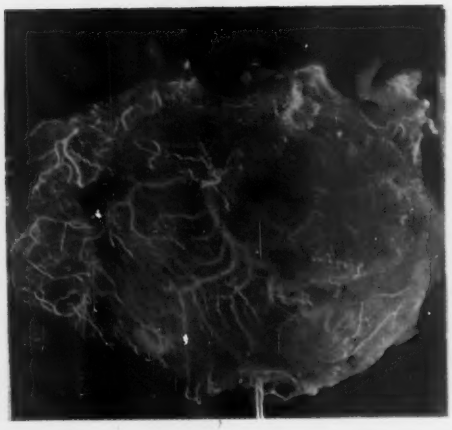

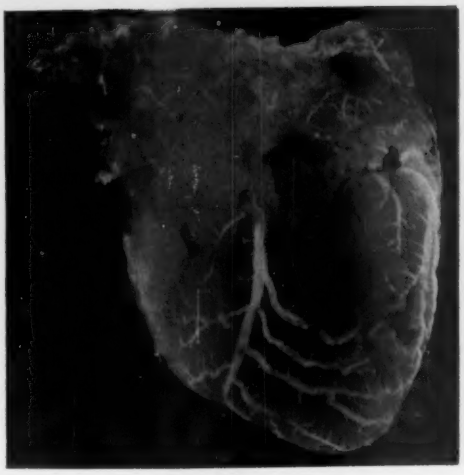

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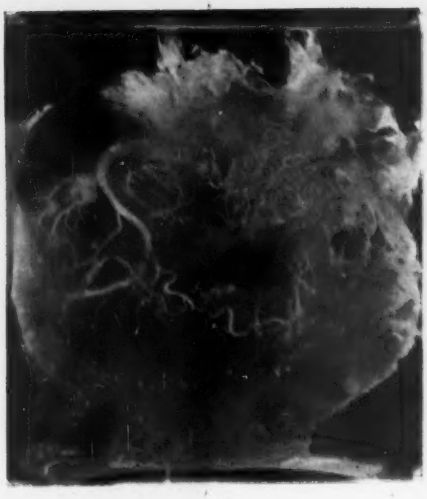

6D

FIG. 6.—Intercoronary communications produced by coronary artery occlusion. Upper left shows a circle of new vessels around the apex of the heart with all three coronary arteries communicating with each other. Note character of new vessels. In upper right, common left coronary artery above the septal branch was completely occluded. Note the new communication from the right to the left circumflex, posteriorly. (C) shows communications between the descending ramus of the left coronary artery and circumflex ramus of left coronary artery. (D) shows posterior aspect of the heart and a communication between circumflex branch of left coronary artery and the right coronary artery.

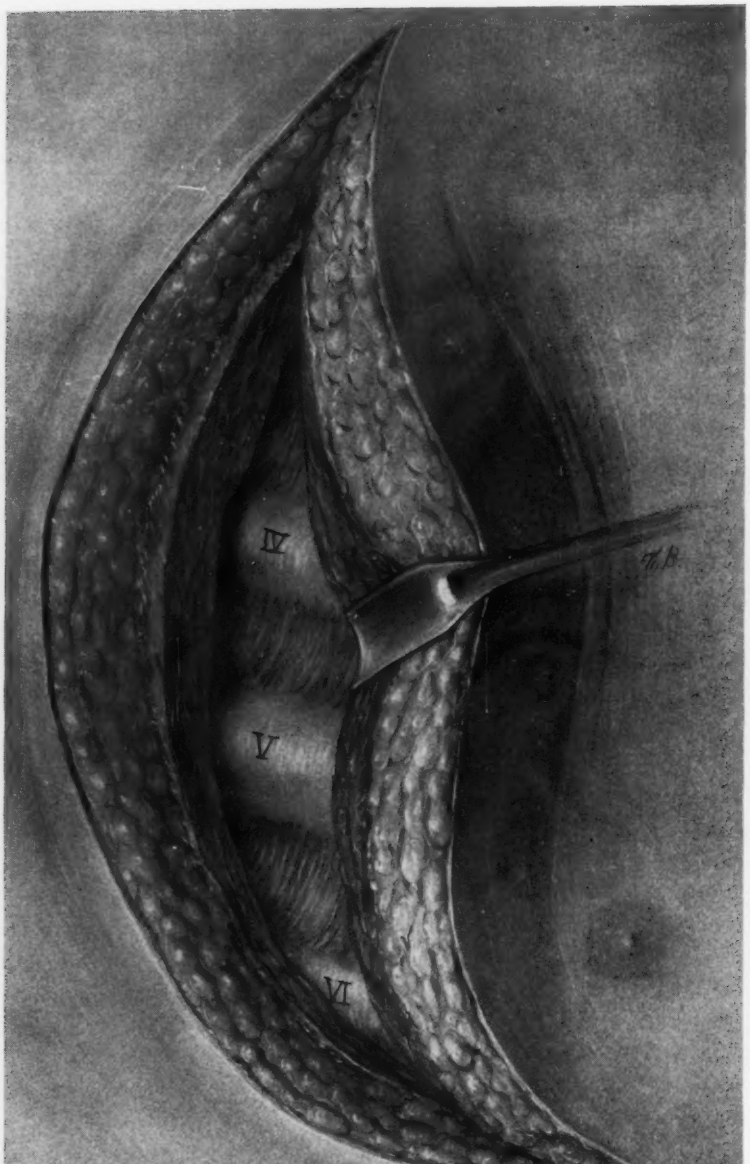

FIG. 7.—Skin incision over the precordium exposing the 3rd, 4th, 5th and 6th costal cartilages.

This, in brief then, is the evidence to support the operative approach to the coronary problem. You will notice that it is all built upon experimental evidence. This is the only foundation upon which I should like to have it built.

The next step is a matter of applying these ideas and methods to patients with coronary artery disease. Let us be reasonable in our attitude towards this aspect of the problem. What kind of patient should we accept for operation? We know that we cannot give a new set of coronary arteries

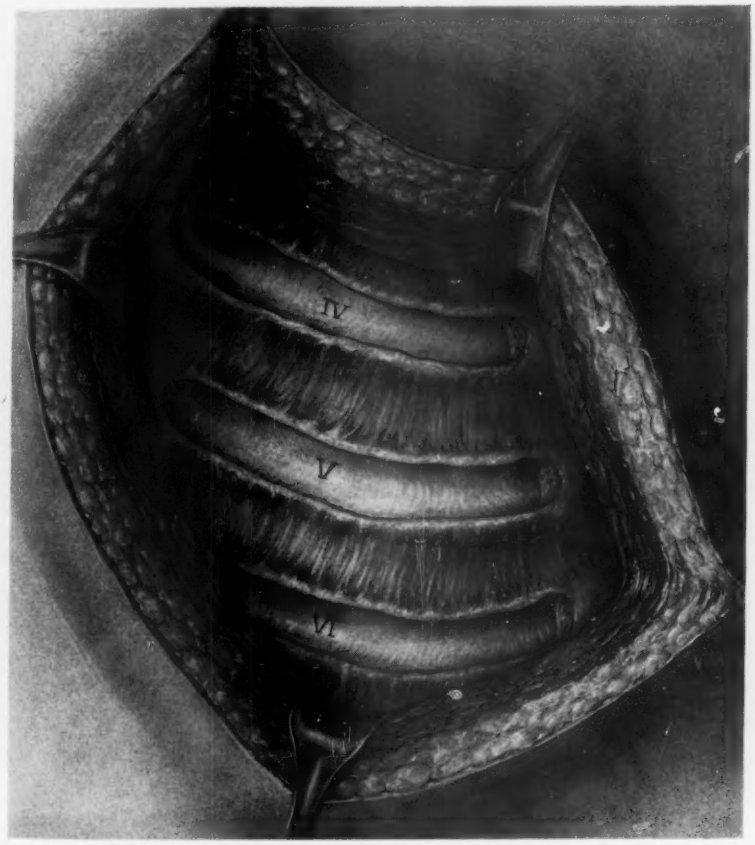

FIG. 8.—Pectoral muscle is retracted. Costal cartilages and ends of ribs removed.

to the heart. We know that we cannot give a new myocardium to the organ. It is clear to me, and I think it must be clear to you, that advanced disease is practically hopeless from the surgical point of view. Early disease with slight irreversible destruction of myocardium is the type of case for operation. The purpose of the operation is to give the heart something that will protect it when occlusion strikes, something that will keep the flame of life from going out. A concise presentation of this matter is given in Tables II and III.

TABLE II

Requirements for Operative Treatment.

1. Localized arterial and myocardial disease require a blood-bath which can be provided by operation and which can prevent:
   a. Infarct formation.
   b. Ventricular fibrillation.
2. Extensive arterial and myocardial disease require a new set of arteries and a new myocardium which cannot be provided by operation.

TABLE III

Classification of Coronary Artery Disease.

1. Trigger types with anoxemic heart muscle which may produce ventricular fibrillation.
   a. Threat to life.
   b. Blood-bath to trigger area is prophylactic.
   c. Types.
      (1) Patients with little or no destruction of myocardium.
         (a) Have the least risk.
         (b) Obtain the best result.
      (2) Patients with definite destruction of myocardium. The amount of destruction determines.
         (a) Risk.
         (b) Result.
2. Non-trigger type with approaching myocardial failure.
   a. Extensive destruction of myocardium.
   b. Optimal period for operation has passed as concerns risk and result.

PRESENT OPERATIVE TECHNIC

I prefer nitrous oxide anesthesia.[4] We have no problem with anesthesia or with respiration. The anesthesia is light and when the operation is completed the patient becomes immediately conscious. The patient is placed in semi-Fowler's position on the operating table. The incision is curved along the left sternal border over the fourth, fifth and sixth costal cartilages and curved laterally along the sixth rib (Fig. 7). The incision is carried through underlying muscle to the third rib and costal cartilages. The fourth, fifth and sixth costal cartilages are removed completely (Fig. 8). A few centimeters of each of these ribs is also removed. The pleura is incised where these structures were removed and the pleural cavity is entered. The tissues between these incisions are left intact. The internal mammary artery is left intact. The inflation of the lungs is regulated so that the left lung comes well up with inspiration and collapses nicely with expiration. The pericardium is then sutured to the precordium in such a way that the heart will not be rotated from its normal position (Fig. 9). The lining of the parietal pericardium everywhere is roughened by special burs (Fig. 10). Powdered asbestos, 0.2 Gm., is then applied to the heart. Some of this is rubbed into the parietal pericardium with a bur and some, mixed with saline, is dripped upon the heart and along the mammary artery and vein. Mediastinal fat is brought in through openings in the parietal pericardium so that it comes into contact with the heart. Fat is probably the best tissue for purposes of vascularization. All tissues that come into contact with the heart serve as grafts. The parietal pericardium is sutured to the chest wall (Fig. 11) so that the heart and the precordium are in contact. The internal mammary artery and the intercostal arteries are in close proximity to the heart. It is advisable not to touch the heart any more than necessary. I do not

like to palpate the coronary arteries to see whether they are sclerotic, although I did this in some of the early operations. There may be some risk in doing this.

Closure is then carried out. The pectoral muscle is sutured where it was incised. Air is removed by suction from the left pleural cavity. Subcutaneous sutures are placed. The skin is closed by suture. Drains are not used.

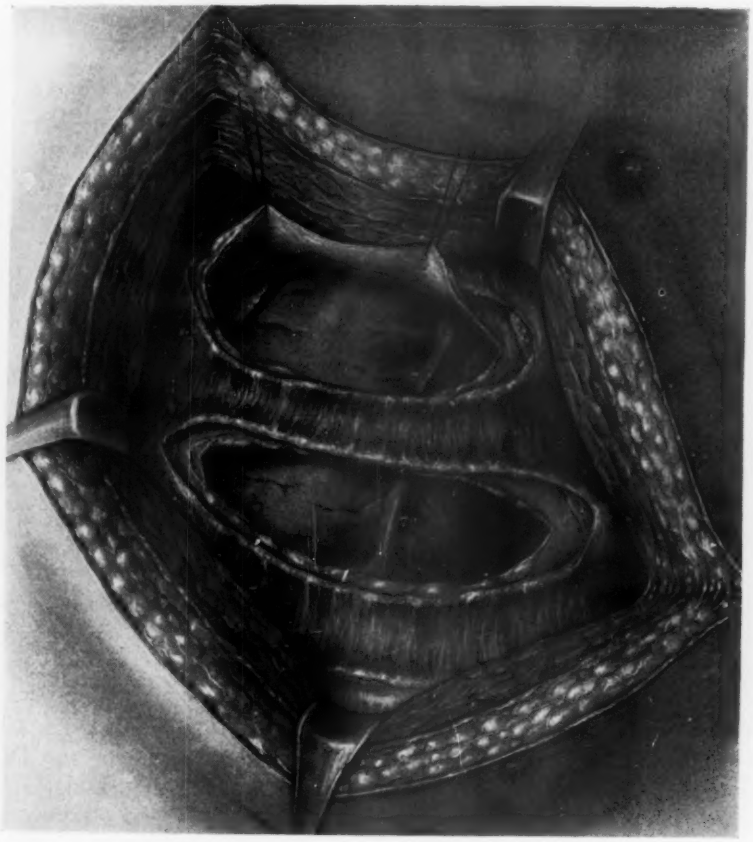

FIG. 9.—Anterior parietal pericardium opened bringing heart into direct contact with chest wall.

The patient is placed in an oxygen tent. Fluid in quantities of three to five liters are given intravenously, daily. We feel that administration of ample fluids may be a factor in avoiding intravascular clotting. Muscle juices absorbed into the blood stream are conducive to postoperative thrombosis, and administration of a reasonable quantity of fluids may help to get rid of this factor. Quinidine is given before and after operation. A test dose of three grains, followed by five grains, is given the night before the operation. An additional dose of five grains is given in the morning before operation. Morphine is given as necessary.

Usually fluid does not collect in the left pleural cavity. If it does form, it can be left to absorb or it can be removed by aspiration.

The operation has undergone several changes since we first carried it out. Originally I used pedicle grafts from the chest wall. I also carried out a bilateral approach in several patients, going in on each side of the sternum. It was my desire to place grafts upon as much of the heart's surface as possible.

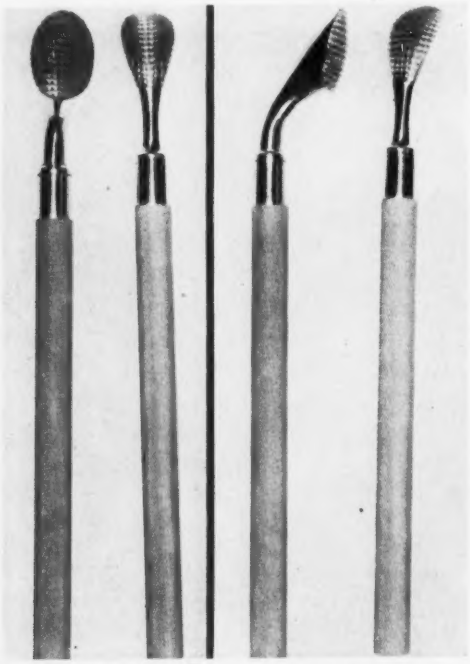

FIG. 10.—Special burs for abrading parietal pericardium.

The operation as outlined above is a procedure of small magnitude. The removal of the bony precordium allows the chest wall, with the mammary artery and intercostal arteries, to come into contact with the heart. Perhaps in the future, a method might be worked out by which an inflammatory agent can be injected into the pericardial cavity and become effective by sealing parietal pericardium and mediastinal fat to the heart. In one of my patients who was in circulatory failure, I removed a costal cartilage under novocain anesthesia and simply introduced an inflammatory agent into the pericardial cavity.

RESULTS OF OPERATION

When it comes to making an evaluation of the operation, one encounters several problems. The most important problem is to determine whether the improvement noted by the patient is due to the operation or whether it would have occurred in the natural course of the disease without operation. We know that the natural course of the disease varies from that of im-

minent death to that of almost full clinical recovery over a period of years. I can think of one or two methods which may help to stabilize interpretation of this variable factor. One method is by the selection of patients whose clinical course is either horizontal or declining over a period of several months. The patient becomes his own control for evaluation of his status before and after operation. When the clinical course has become

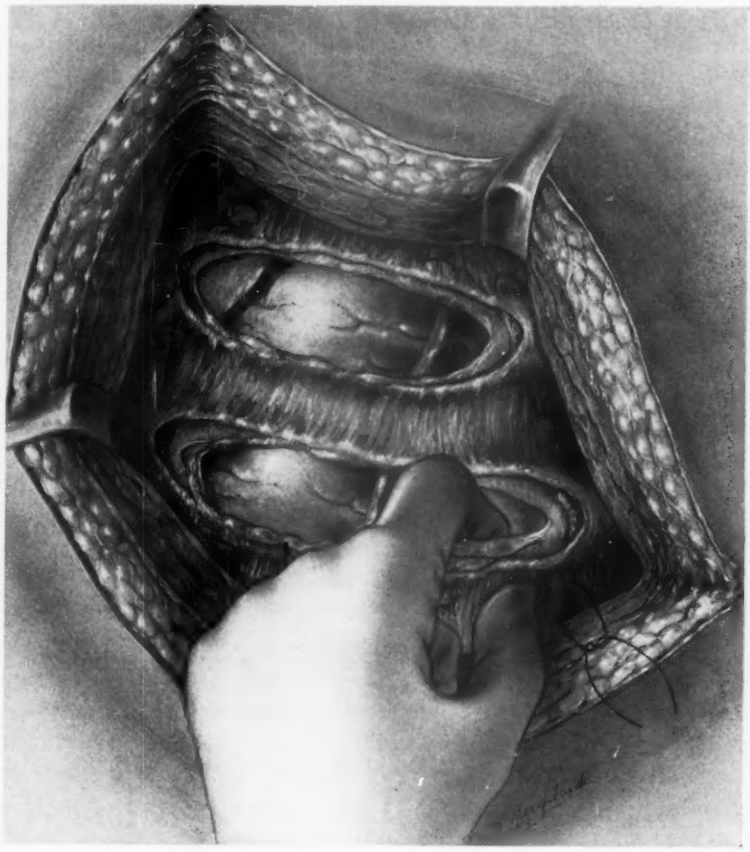

FIG. 11.—Pericardial pericardium sutured to chest wall by about ten sutures. Powdered asbestos, 0.2 Gm., placed on the surface of the heart and also over the tissues in contact with the heart.

more or less stabilized we can interpret improvement in the clinical course as having been produced by the operation. However, we cannot be absolutely secure in this deduction. It is still possible that the improvement might have occurred without the operation. Another method by which the result of the operation can be determined is to get what we might call a group experience. If each patient in the group followed a pattern after operation, the evaluation would be more simple. But we must allow for variables in the group. The occlusive nature of the disease may be progressive or it

may be quiescent for a time and then become progressive. It is also possible to have patients in the group who have extensive and irreversible disease of the arteries and myocardium. Such patients, even though they are fortunate enough to survive, may get little or no improvement from the operation. Such patients belong to an inoperable group, but it is almost impossible to recognize them clinically so as to avoid operating upon them. It might also appear to be possible to evaluate results of operation by having two groups of patients going along side-by-side, one group with the operation and the other group without the operation. We could compare clinical results including pain, exercise tolerance, duration of life, *etc.* Such data would be valuable, but at the same time we must recognize the fact that it is impossible to get two identical groups of patients. It seems to me that the best way to get measurements on the effectiveness of the operation is to take patients whose clinical course has become stabilized and let each patient become his own control. *It is possible for us to err in either direction by making evaluations that are not justified and by refusing to make evaluations that are justified. One mistake is quite as serious as the other.*

There are two considerations that come to our aid in the evaluations of results: One is the knowledge gained by experimental work; the other is the information gained by examination of the heart after the patient dies, and interpretation of the clinical result in terms of the specimen. Without these aids I should almost refuse to make a clinical interpretation of result. This conservative point of view, I believe, is necessary until the operation becomes established as a recognized form of treatment. To illustrate this attitude I might mention the fact that some patients stated that they felt better as early as one week after operation. Tichy and I had no explanation for this early improvement from the laboratory, and we refused to place any significance in these statements of improvement. Later we found, in the laboratory, that intercoronary communications were demonstrated as early as five days after operation and, with this as an aid, we are now willing to accept early improvement as being significant. Likewise, we have had the opportunity of interpreting the clinical course in terms of the specimen after death of the patient. One of these patients was able to work as a salesman after operation. He felt much better. Two years and three months after operation he died from a cerebral hemorrhage. Examination of the heart showed a number of vascular communications between the heart and the grafts (Fig. 12). The cleared specimen is very significant in that, in my estimation, it can account for the clinical improvement of the patient. This is the best proof that I can give that coronary artery disease can be helped by operative methods.

I think the patient is able to make an accurate appraisal of the results of the operation. It is the patient who feels the pain and who knows whether his ability to get around has been improved. Appended are statements from

some of the patients made within the past few months concerning their present status:

"Feeling fine and able to work hard every day." (Operation 2-13-35)

"My condition is very good considering everything. The heart is going along well and I believe I may live for several years, if some other trouble does not take me out of circulation." (Operation 7-9-35)

"I have had seven years of borrowed life due to your wonderful skill and loyal interest in my case. I am working every day." (Operation 2-22-36)

"I do a hard day's work in the machine shop everyday. I haven't missed a day's work for a long time. I feel fine and have no trouble." (Operation 11-18-36)

"I am still coming along in great shape and feel equal to about any occasion. I am well pleased with my condition. Feeling fine and able to work." (Operation 12-3-36)

"The angina pain bothers me after meals, exertion and excitement, very seldom at rest. I feel, however, that I have been greatly helped by the operation." (Operation 1-30-37)

"At present, and for the past three years, I have been working as a chef. I work very hard but feel no ill effects from it. I use absolutely no medication of any kind and I am not under any medical care." (Operation 1-30-37)

"I feel fine. I have no trouble with my heart." (Operation 3-6-37)

"I have been feeling fine; eat anything and everything, and as much as I want, without distress. I walk up and down stairs; get on and off street cars before they stop, *etc.*, with no discomfort. I go to the stock market every day, which is equivalent to work, and it does not affect me. I feel sure that the operation saved my life and I expect many more years of continued good health. Most of the time I don't know I have a heart—going great!" (Operation 4-24-37)

"I was a principal in the Public Schools before I developed this condition and became totally incapacitated. I was confined to my room for a year and could walk no farther than from the bedroom to the bathroom without pain. I experienced early benefit from the operation, and, at present, am feeling well, enjoying life and able to do a moderate amount of work." (Operation 7-30-37)

"In Florida since November 1, 1942, and expect to remain here until May 1, when I expect to return to work. Am much better—nerves, heart action and frequency and severity of spasms much improved and I expect to continue to improve." (Operation 8-4-37)

"In general, pain since operation is about one-quarter its previous frequency and severity." (Operation 8-13-37)

"I have gained much strength since the operation and find I do not tire nearly as easily as before. I have no pain around the heart. I have none of the old symptoms since the operation. I feel that I have been fortunate in having the operation made available to me. I have not yet returned to work, following the advice of Doctor Beck at the time of operation, to the effect that I should wait about six months thereafter before attempting to work. This period will not be up until about May 1st." (Operation 10-30-42)

"I do feel improved over that of a few weeks ago. I would say that, offhand, I feel about 75 per cent of what I felt preoperatively. I expect to improve steadily though—and realize it takes time. I walk around, drive a car and do mild recreational exercises." (Operation 1-17-43)

Other Investigations.—O'Shaughnessy[5] was the first to take up the work of revascularization of the heart after we had begun our studies. He used omentum for his grafts and brought it through an opening in the diaphragm and applied it to the apical region of the ventricles. After per-

forming experiments upon animals he applied the procedure to patients, beginning in January, 1936. He claimed originality for the idea of cardio-omentopexy, as he called it, although Tichy and I used omentum in our experimental work beginning in 1932. Herniations developed in several of our experiments and we did not apply this procedure to patients. O'Shaughnessy demonstrated one specimen, from a dog, in which barium was injected into the vessels of the graft and it appeared in the coronary arteries. This was confirmation of work that we had done. He also presented microscopic evidence of blood vessels in the grafts, but such communications have no significance relative to the amount of blood that might be going across such adhesions. His experimental evidence, by itself, can scarcely be regarded as convincing evidence that the operation should be undertaken upon patients. The results with the patients were reported by him as beneficial.

W. F. Rienhoff, Jr.,[6] of the Johns Hopkins Hospital, in a discussion of this work stated as follows: "Independently, and without any knowledge of Doctor Beck's experiments, or interest in this problem, we began, in October, 1934, investigating different methods of supporting an interrupted coronary circulation. We have used a series of old dogs for the reason that the independent development of a collateral circulation in younger animals is so readily achieved that recovery from ligation of the right or left anterior descending coronary artery may be clinically uneventful and easily survived by the animal. Doctor Beck did not state whether his series of dogs were young or old. In a small series of nine dogs, the epicardium was then moistened with half strength iodine and the omentum wrapped, so to speak, completely around the heart, entirely covering the anterior surface. Three to six weeks later, ligation of the entire left coronary artery just below its origin from the aorta and above the division into the left anterior descending and circumflex arteries was accomplished by taking a deep bite with a No. 2 French needle in the ventricular wall in the region of the left coronary artery just beneath the tip of the left auricle. The distension of the coronary veins distal to the ligature proved its location. No disturbance in cardiac rhythm followed these ligations after previously performed cardio-omentopexy, either clinically or in the electrocardiogram. The dogs were not at all ill. Whereas, before similar ligation was invariably fatal, not one animal succumbed after adhesion of the omentum to the heart had been produced. These specimens will be reported on later."

I have the following comment to make about this discussion. We have never found any difference in the coronary bed in dogs, whether the dogs are young or old. In the normal heart the coronary arteries are essentially end-arteries, regardless of the age of the dog. There are certain slight variations in intercoronary communications that are present in a group of specimens but these variations, slight as they are, are the same regardless

of age. My associates and I have not found age to be a factor in mortality after coronary artery ligation. I found tincture of iodine to be a strong necrotizing agent and too dangerous to use. There is no coronary vein in the location of the common left coronary artery. The vein is several millimeters below the bifurcation of this artery. If the artery is ligated, the vein is not ligated by the same suture; if the vein is ligated the artery is missed in this suture. We have never been able to ligate the common left coronary artery in one step, with recovery, regardless of the method used for protection of the heart before this was done.* On the basis of our experience, I do not believe this can be accomplished in one stage. It is difficult to accomplish complete occlusion of this artery by repeated steps. We have accomplished this a number of times and it requires considerable care not to take the artery down abruptly in any one operation, thereby producing death of the animal. It also requires weeks or months between operations for intercoronary channels to develop so that an additional step in the occlusive process can be tolerated. There is no reference in the Quarterly Cumulative Index Medicus to a subsequent report of these experiments by Rienhoff.

Burchell[7] carried out experiments in which grafts were placed upon the heart and the coronary arteries were occluded. A quotation from his work is as follows: "So far as these studies on coronary occlusion in dogs are concerned, the rôle played by vascular channels in pericardial adhesions in supplying blood to the myocardium has been minimal or nonexistent. The possibility that the small vascular connections, between a graft and the heart might develop to a functioning value cannot be denied, but in the experiments seemingly favorable to such a result it has not occurred." In making this analysis of his own experimental work, Burchell was not urged by a desire for independent accomplishment. He was critical throughout, and, I think, he was essentially correct. However, I think if he had gone farther with his experimental effort he, no doubt, would have demonstrated anastomoses such as are illustrated in the present communication.

Heinbecker and Barton[8] carried out experiments in which a mixture of gelatin, aleuronat, starch, glycerin, water and lionite was introduced into the pericardial cavity. In some experiments these authors also used sodium morrhuate. After these substances were introduced the pericardium was closed and then the pericardium was sutured to the retrosternal tissues. Fourteen animals were prepared in this manner. Four to 12 weeks later these animals were again operated upon and the descending ramus and the circumflex ramus of the left coronary artery were ligated about one centimeter from the aorta. Eight of the 14 animals died and six survived. Infarcts were not found in these specimens.

We carried out experiments in which we tried to repeat this procedure. We were not able to get any animals to survive ligation of both of these arteries in one step. It would be highly desirable if Heinbecker and Barton

would repeat these experiments and inject the coronary arteries and clear the specimens. These ligations are very much greater than anything that any of my associates or myself have been able to accomplish.

Thompson and Raisbeck[9] carried out experiments in which talc was introduced into the pericardial cavity and they applied this procedure to patients with coronary artery disease. These authors found that the mortality following coronary artery occlusion was reduced by the use of the talc. They found that ligation of the descending ramus of the left coronary artery and vein at a point one centimeter below the origin of this artery carried a mortality of 50 per cent. A similar ligation was performed, but, in addition, talc was introduced into the pericardial sac at and around the site of ligation. Here the mortality was 25 per cent. In another group of experiments talc was introduced and, two or three weeks later, a similar ligation of the artery was done—there was no mortality.

We studied the effect of talc, and repeated these experiments. We were not able to obtain the same beneficial results as these authors reported. We also found that powdered asbestos produced a much more vascular type of reaction than did talc.[3]

Reference should be made to the work on coronary vein ligation. Ligation of corresponding vein and artery, as compared to ligation of artery alone, is a subject that has received much study by surgeons. These studies concerned the femoral artery and vein and also the vessels to the upper extremity. Gross, Blum and Silverman[10] applied the idea of vein ligation to the heart. They ligated the coronary sinus and found that this procedure was beneficial, in that the amount of muscle destroyed following arterial occlusion was less in extent when artery and vein were ligated as compared to results when artery alone was ligated. These authors did not find that vein ligation reduced mortality of arterial ligation. However, Fauteux[11] found that if he ligated the magna cordis vein and then ligated the descending ramus of the left coronary artery that the mortality was very much less than if he ligated only the artery. Beck and Mako[12] studied this subject and found that in the experiments in which the artery was completely occluded there was no definite difference in the size of the infarct whether the vein was or was not occluded. This did not seem to be the case when the artery was only partially occluded instead of completely occluded. In these experiments it appeared that ligation of the vein did reduce the size of the infarct as compared to the infarct following partial occlusion of the artery alone. Mako and I concluded that the beneficial effect following vein ligation was probably not great enough to justify application to patients. We could not obtain the good results reported by Fauteux. Recently Fauteux reported an operation upon a patient with sclerosis of the descending ramus of the left coronary artery in which he ligated the magna cordis vein. The physiology of this subject has been studied by Gregg, and his associates, in Wigger's laboratory.[13]

The query might be raised as to why certain investigators were able to accomplish so much in the way of coronary artery ligation. I believe a partial answer can be given to this query. One explanation concerns the site of the ligature. If this varies in different experiments the results will vary, because one or two arterial branches may be missed in some experiments if they come off proximal to the ligature, and these branches make a difference in the result. Another explanation lies in the method of producing the ligation. A suture placed in the region of the artery without dissection of the artery may well miss the artery, as I think must have been the case with Rienhoff. He used the location of the magna cordis vein, and the distension of this vein, to tell him whether the artery was occluded, and he did not report on the facts as found in postmortem examination of the specimens. Another explanation, no doubt, is related to the natural enthusiasm and desire for accomplishment on the part of the investigator. This may be a real factor, especially in the early developmental period, after we did our first experiments. It is so easy to over shoot the mark! Of course, the reader must remember that without enthusiasm none of this experimental work would have been undertaken. I would gladly welcome the accomplishments as set forth in some of the reports. My associates and I have tried over and over again to improve the preparation of the heart so that it could tolerate occlusion of the descending ramus of the left coronary artery and the circumflex branch of the left coronary artery in one step. If the heart could be so prepared then, indeed, we would have a very good method for the treatment of coronary artery disease in patients. We can accomplish something in the way of arterial ligation but it is not that much. No doubt the methods for preparation of the heart can and will be improved by future experimentation.

SUMMARY AND CONCLUSIONS

1. The surgical approach to the treatment of coronary artery sclerosis has been established upon a scientific basis. Coronary artery disease is compared to epilepsy. The trigger in the heart "fires" or discharges and produces a state of incoordinated contractions and relaxations of the heart muscle fibers. This is the well known "heart attack" and is fatal. A small amount of blood to the zone of anoxemia can prevent the trigger from "firing." This may be regarded as a blood-bath and can be produced by operative methods.

2. A study group of 30 patients with coronary artery disease were operated upon. The patients who recovered from the operation were partially or completely relieved of pain. Their ability to get around has been increased; some of the patients are doing hard physical work.

3. The operation can be considered as a procedure in therapy.

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CLINICAL APPRAISAL OF THE BECK OPERATION*

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THE NATURAL HISTORY OF PATIENTS with coronary sclerosis, with and without myocardial infarction, varies greatly, but the average life expectancy is brief. In Table I are compiled the average duration of life after the onset of symptoms as determined by several observers.

TABLE I

Observer	Number of Patients	Average Duration of Life after Onset of Symptoms (In Years)
MacKenzie[1] (angina pectoris)	213	5.4
White and Bland[2] (angina pectoris)	213 patients dead	4.4
	273 patients living	5.1
	486 total	4.9
(coronary thrombosis)	101 patients dead	1.5
	94 patients living	2.4
Wedd and Smith[3] (angina pectoris)	166 patients	5.8
Levine[4] (coronary thrombosis)	101 patients dead	3.4
	271 patients living	2.3
Feil[5] (angina pectoris)	100 patients (private)	4.5
(coronary thrombosis)	256 patients dead	
Lakeside Hospital	Autopsy performed	1.1 (See Fig. 1.)

In Figure 1, 256 cases of myocardial infarction are tabulated according to the duration of life from the onset of symptoms. These patients received conventional medical treatment but medical treatment is, at best, palliative. Medical therapy does not in any way alter either the underlying pathologic changes in the coronary arteries nor does it stay the progress of these changes. The surgical approach of attempting to improve the coronary artery circulation is fundamental. Knowing the grave prognosis of patients suffering from coronary artery sclerosis, the operation of Beck's was a welcome addition to therapy. Beck's operation, described in previous papers,[6] consists, essentially, of increasing coronary circulation by producing inflammation on the surface of the heart and implanting grafts upon the heart. Thirty-seven patients comprise the basis of this paper. Two previous reports on some of these patients have been made.[7, 8]

Types of Patients Selected for the Operation.—The first patients who were operated upon were for the most part suffering angina on slight exertion. Because of the serious coronary disease and the associated pathologic changes (generalized arteriosclerosis, myocardial fibrosis) the operative

* Submitted for publication October 11, 1943.

mortality was high. As the operative technic was further improved, patients were selected with less severe coronary disease and without complicating factors. The diagnosis of coronary artery disease was definitely established and other pathologic conditions simulating the symptoms of angina were ruled out. Hypertension was not alone a contraindication. Diabetes, if present, was under control. The age of the patient was an important factor in selection —the younger the patient, the more favorable the outcome, although one of the best results of the series (Case 20) was 70 years of age. Pulmonary

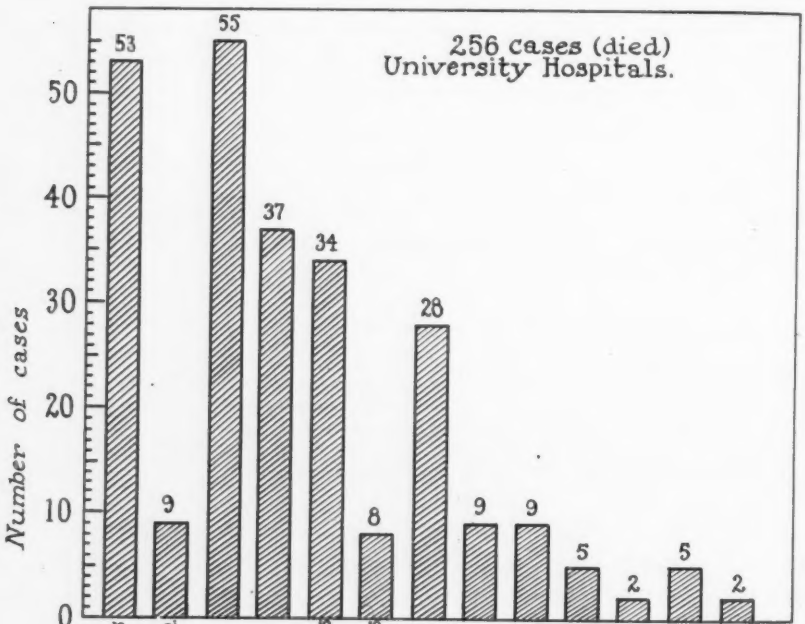

FIG. 1.—Tabulation of 256 cases of myocardial infarction, according to the duration of life from the onset of symptoms.

disease (severe emphysema, chronic bronchitis, bronchiectasis) was of course a contraindication. Obesity increased the operative hazard, although some of the successful cases were overweight.

Postoperative Course of Patients. Twenty-three patients (62.2 per cent) survived the operation and have been followed. Fourteen patients are still alive of whom nine are in excellent condition and five are in good condition, not completely relieved of symptoms but who have increased exercise tolerance (Table II).

TABLE II—JULY 1, 1943

Case	Age	Survival Period		Living	Dead	Condition After Operation
		Years	Months			
1	56	8	5	+		Excellent*
3	53	2	6		+	No improvement
4	57	8	0	+		Good†
6	61	6	1		+	Excellent
9	51	5	8		+	Excellent
11	49	7	4	+		Excellent
13	58		6		+	No improvement
15	54	6	0		+	Excellent
17	56	6	7	+		Excellent
18	53	5	1		+	Excellent
19	55	6	7	+		Excellent
20	70	2	3		+	Excellent
21	57	6	5	+		Good
22	48	6	5	+		Excellent
23	55	6	4	+		Good
24	47	1	3		+	Little improvement
25	57	6	2	+		Excellent
26	56	5	11	+		Excellent
27	53	5	11	+		Excellent
28	55	5	10	+		Good
31	54		4		+	No improvement
36	59		9	+		Excellent
37	35		6	+		Good

*Excellent: Sufficient improvement to permit patient to return to his former occupation, with no or minimal symptoms.

†Good: An increase in exercise tolerance and diminution in symptoms.

SUMMARY OF PATIENTS NOW LIVING

Case 1.—Arteriosclerotic heart disease and angina pectoris of nine years' duration; severe for five years; moderate generalized arteriosclerosis with hypertension; arterial pressure 169/92. Moderate chronic pulmonary emphysema. A 48-year-old farmer, with gradually diminishing exercise tolerance, finally became incapacitated for any work because of retrosternal pain, fatigue and dyspnea. Operation was performed February 13, 1935. Four months later he began to do light work around the hospital as a gardener and made 82 trips on the steps without pain, stopping because of dyspnea. It is now eight years and five months since the operation and he is able to work 12 hours daily as a farmer. He feels no more than the usual fatigue at the end of the day. The result in this, the first patient to have the operation, is excellent.

Case 4.—Arteriosclerotic heart disease, coronary sclerosis and angina pectoris of four and one-half years' duration; generalized arteriosclerosis and diabetes mellitus. A surgeon, age 50, with angina of effort and emotion, was totally incapacitated in December, 1932. Subtotal thyroidectomy was performed in January, 1933. He had a coronary thrombosis in February, 1933. The patient had had diabetes mellitus since 1918, requiring insulin. He had had pain in the legs for three years on walking. A roentgenogram of the legs showed calcification of the vessels. The electrocardiogram showed a deep Q_3. Operation was performed July 9, 1935. The exercise tolerance increased from 18 trips before operation to 32 trips after operation. The patient has less pain on exertion and exposure to emotional stress. The results in this case are classified as good.

Case 11.—Arteriosclerotic heart disease and angina pectoris for 11 months; probably coronary thrombosis at onset of illness. A tailor, age 42, had angina of effort and emotion. He became totally incapacitated. Rest and drugs failed to do more than give

relief. Angina was produced by 24 trips on the steps. After glyceryl trinitrate he was able to make 42 trips before angina occurred. The limb-lead electrocardiogram was normal but the T wave in Lead 4R was negative. Operation was performed February 22, 1936. The patient is now able to work. He can tolerate 97 trips on the steps and stops because of dyspnea and not because of pain. The result in this case is excellent.

Case 17.—Arteriosclerotic heart disease and angina pectoris; myxedema and secondary anemia. A machinist, age 50, had had a typical history of angina of effort for 18 months. The basal metabolic rate was —30 and the patient took small doses of thyroid. The electrocardiogram revealed left axis deviation and QRS of normal voltage; the T wave was almost iso-electric in all leads, including the chest lead. Operation was performed November 18, 1936. Congestive heart failure developed after operation and cleared up with appropriate treatment. Tolerance for exercise increased from 36 trips on the stairs before operation to 50 trips after operation. The dose of thyroid extract has been increased to ¼ grain. He does not take any nitroglycerin. He is working at his job as machinist. It is now six years and seven months since the operation was done. The result is excellent.

Case 19.—Arteriosclerotic heart disease and angina pectoris of 17 months' duration. A coal miner, age 49, was totally incapacitated during the entire course of his illness. He had severe pain at rest and morphine was given for the pain. Theophylline with ethylendiamine and glyceryl trinitrate gave no relief. The electrocardiagram showed alterations indicative of a remote posterior and basal infarct. Operation was performed December 3, 1936. Marked improvement followed operation. He is able to do much work on his farm. It is now six years and seven months sinced the operation and the result is excellent.

Case 21.—Arteriosclerotic heart disease and angina pectoris of five years' duration; mild diabetes mellitus. A clerk, aged 51, failed to benefit from medical treatment; paravertebral injection with alcohol failed to give relief and he became totally incapacitated for work. The left ventricle was slightly enlarged. The peripheral arteries were calcified. The electrocardiogram was normal at rest but after exercise showed definite alterations from normal. Operation was performed January 20, 1937. The patient was much improved following operation. The pain did not completely disappear but became less severe. He returned to work but was forced to retire because of parkinsonism.

Case 22.—Arteriosclerotic heart disease and angina pectoris; thromboangiitis. A cook, age 42, had angina of effort and emotion for five and one-half years and was incapacitated for his work for two years. He took morphine for the pain. The left foot was cool, and the arterial pulse was not palpable in the left leg. The electrocardiogram showed no significant changes before or after exercise. Operation was performed January 30, 1936. He had several angina attacks in the early postoperative period. Later he showed striking improvement. He is at work as a chef and does not require medication. The result is excellent.

Case 23.—Arteriosclerotic heart disease and angina pectoris of six months' duration. A molder, age 49, had a typical history of angina of effort for six months and had to give up work for four months before admission. Medical care with a long rest in bed did not increase his tolerance for exercise. The anginal syndrome was produced by 53 trips, and after glyceryl trinitrate he was able to make 90 trips. Electrocardiographic changes were present during the induced angina. The circulation time was 20 seconds. Operation was performed March 6, 1937. The patient states that he has felt better since the operation and he is able to make 52 trips on the steps, stopping because of

moderate dyspnea. He works in his garden and does much physical work about the house without symptoms. We regard his results as good.

Case 25.—Arteriosclerotic heart disease and angina pectoris of nine years' duration. A retired salesman, age 52, had some attacks which were sufficiently severe to have been caused by coronary thrombosis. The conventional electrocardiogram was normal, but the T wave in the chest lead was reversed in direction. The record taken during the induced anginal attacks after exercise showed changes suggsting a posterior and basal infarct. Operation was performed April 24, 1937. The patient states that there is definite improvement and that he is able to carry on his work, without symptoms. The result in this case is excellent.

Case 26.—Arteriosclerotic heart disease and angina pectoris for one and one-half years; an attack of myocardial infarction one year before operation. A female school principal, age 50, had severe angina of effort and of emotion which totally incapacitated her. She was able to make but three two-step trips, stopping because of typical angina. Operation was performed July 30, 1937. Her convalescence was slow, but on October 11, 1937, she was able to make 12 trips, and on November 29, 1937, this was increased to 20 trips. In the intervening period, the patient has been able to walk a few blocks without pain. The result in this case is excellent.

Case 27.—Arteriosclerotic heart disease and angina pectoris following an attack of coronary thrombosis two years previously. A factory superintendent, age 48, had angina of effort which caused him much distress. He was operated upon August 4, 1937, and his convalescence was uneventful. He left the hospital in 37 days. He was able to return to his job, working five to eight hours a day. The result is excellent.

Case 28.—Arteriosclerotic heart disease and angina pectoris of six years' duration. A salesman, age 50, was unable to carry on with his work, and he was operated upon August 13, 1937, making an uneventful convalescence. He gradually improved and finally was able to do moderate exercise without pain. He has shown definite improvement. We regard the result in this case as good.

Case 36.—Arteriosclerotic heart disease with angina pectoris. A male, age 39, a railroad dispatcher, had typical angina of effort for nine months. He was put to bed for four months but continued to have symptoms on effort. Blood pressure 106/74. The electrocardiogram showed right bundle branch block and an absence of a positive deflection in all "V" chest leads, 1–5. There was positive deflection in V_6. T was inverted in $V_{3, 4, 5}$. The record suggested old anterior and apical infarction as well as septal infarction. He is now able to walk several miles at a brisk rate without symptoms. He has returned to work. His electrocardiogram is unchanged. It is now nine months since the operation and the result is excellent.

Case 37.—Arteriosclerotic heart disease with angina pectoris; rheumatic heart disease; mitral valvulitis with insufficiency. A male, age 35, physician, had angina of effort and of emotion for two and one-half years. This pain followed an episode diagnosed as coronary thrombosis although there was no electrocardiographic evidence. The heart was normal in size, but there was a moderately loud systolic murmur at the apex. This murmur had been detected for many years. Blood pressure 132/94. The chest lead in the electrocardiogram showed inversion of T after exercise. He was operated upon January 17, 1943, and made an uneventful convalescence. He has returned to his practice. It is now six months since the operation and he has less pain. He feels that the operation has given him definite improvement. The result is classified as good although the time has been too short to make a definite appraisal.

PATIENTS WHO WERE OPERATED UPON AND HAVE SINCE DIED

Case 3.—An executive who after operation showed some improvement but continued to have pain.

Case 6.—A mechanic with severe generalized arteriosclerosis. He was much improved after operation and was able to work. He had some recurrence of his angina but lived six years and one month after operation.

Case 9.—A painter who lived five years and eight months after operation. He was greatly improved and was able to return to work, working up to the time of his death.

Case 13.—A bookkeeper who had left ventricular failure previous to operation. He did not improve and died six months later of coronary failure.

Case 15.—A manager of a store who was very greatly improved by operation. He continued to have some angina of effort. He continued to work and died six years later.

Case 18.—A cook who was greatly improved and returned to his work. He died five years and one month after operation of acute coronary insufficiency.

Case 20.—A book agent, the oldest of the series, improved after operation sufficiently to return to his work. He died two years and six months after operation of cerebral hemorrhage.

Case 24.—A tailor, who, after operation, continued to have angina and showed little improvement. He died one year and three months after operation of coronary thrombosis.

Case 31.—This patient showed no improvement after operation, and died four months later of acute coronary insufficiency.

Operative Mortality.—There were 14 operative deaths, or 37.8 per cent (Table III).

TABLE III

Case	Age	Days Lived	Cause of Death
2	53	6	Thrombosis of abdominal aorta
5	58	2	Mediastinitis (*Cl. welchii* infection)
7	57	4	Cerebral hemorrhage; bronchopneumonia
8	53	1	Coronary thrombosis
10	56	2	Coronary insufficiency, acute
12	54	9	Bronchopneumonia
14	53	5	Bronchopneumonia
16	57	1	Coronary insufficiency, acute
29	50	2	Bronchopneumonia
30	54	0	Coronary insufficiency, acute
32	58	0	Coronary insufficiency, acute
33	44	12	Coronary insufficiency, acute
34	56	2	Bronchopneumonia
35	64	2	Coronary insufficiency, acute

CASE WITH SEVERE CORONARY ARTERY DISEASE AND RECENT AND REMOTE MYOCARDIAL INFARCTION

Case 33.—Male, age 44, had angina of effort for ten years. His pain had increased greatly during the six months before operation. One and one-half hours after operation he had an attack of severe retrosternal pain, with dyspnea. He was given morphine and papaverine intravenously and atropine sulfate hypodermically. His symptoms gradually subsided in 24 hours. His convalescence was satisfactory until the seventh postoperative

day, when he had severe inspiratory pain in the right chest. Later a pleural friction was heard. Thirty-six hours later another episode of pulmonary infarction occurred. On the tenth, eleventh and twelfth postoperative days he had severe retrosternal pain, dying on the twelfth postoperative day. The limb electrocardiograms showed elevation of R-T in all leads. No chest leads were taken after operation. The electrocardiogram taken a few hours before death showed typical changes of an acute *cor pulmonale.*

Autopsy.—The postmortem examination revealed subintermural hemorrhage in the wall of the main left coronary artery and recent thrombosis of the ramus descendans left. There was recent infarction of the entire I-V septum. Remote thrombosis of the right coronary artery was found with remote infarction of the midlateral portion of the left ventricle. There were mural thrombi in the right auricle and in the apex of the left ventricle. Thrombi were also found in the branch of the right pulmonary artery to the right lower lobe. There was a recent infarct of the left kidney.

This patient illustrates the difficulties involved as the result of widespread coronary artery disease and the additional complications of pulmonary infarction and myocardial infarction following operation.

Postmortem Studies. Nine patients dying, but who survived the operation from four months to six years (Table IV); came to autopsy. In all instances severe coronary disease was found.

TABLE IV

Case	Age	Survival Period		Cause of Death
		Years	Months	
3	53	2	6	Coronary insufficiency
6	61	6	1	Myocardial failure
9	51	5	8	Acute myocardial infarction
13	58		6	Myocardial failure
15	54	6	0	Coronary insufficiency
18	53	5	1	Coronary insufficiency
20	70	2	3	Cerebral hemorrhage
24	47	1	3	Acute myocardial infarction
31	54		4	Coronary insufficiency

DISCUSSION.—The prognosis in cases of coronary artery disease varies greatly but, on the average, it is grave and the life expectancy is relatively short. The surgical means of producing an augmented coronary circulation is the first attempt to relieve patients of symptoms and to increase length of life. As has been stated by Beck, there must be sufficient good myocardium to maintain life or the improved coronary artery circulation will be ineffectual. Therefore, the candidates for the operation should be carefully selected, both as to extent and degree of coronary artery sclerosis and as to associated pathologic conditions.

It may be suggested that most of the cases with severe coronary artery disease did not survive the operation, and that those surviving did not improve. From postmortem examination of the patients who survived but who died subsequently, severe and widespread coronary artery disease

was demonstrated (Table IV). Cases 6, 9, 15, 18, 20, were greatly improved and were able to return to their accustomed jobs.

In the 37 cases here reported the results of the operative survivals—both the patients who have since died and those who are still living—have been favorable in a large percentage of the cases. The favorable effect of the long bed rest following operation may have played a part in the immediate result. The total duration of life from the onset of symptoms and from the operation is found in Table V. The operative mortality in the first 17 cases was 47 per cent; in the second 17 cases it was 35.3 per cent. Patients should be selected for operation earlier in the course of the disease. The mortality should be low in this type of case.

TABLE V

Patients	Number	Per Cent	Average Duration of Life from Onset of Symptoms	Average Duration of Life Following Operation
Still living	14	37.8	9.0 years	6.9 years
Lived 4 months to 6 years	9	24.4	8.9 years	3.9 years
Dying postoperatively	14	37.8	4.1 years	

SUMMARY

1. Thirty-seven patients with coronary artery sclerosis and angina pectoris were operated upon by the Beck technic of providing additional blood supply.

2. There were 14 postoperative deaths (37.8 per cent).

3. Nine patients who survived the operation, but died from four months to six years later, were studied after death. The results in these patients were: Excellent—5; little or no improvement—4.

4. Of the 23 patients who survived the operation, 14 are still living. Of these nine are definitely improved and five show an increase in exercise tolerance and diminution in symptoms.

5. Of the 23 patients who survived the operation, the results were as follows: Excellent—14, or 60.9 per cent; good—5, or 21.7 per cent; little or no improvement—4, or 17.4 per cent.

6. The operation has given great relief to the 14 survivals. Five of the patients who subsequently died were greatly benefited.

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TOTAL GASTRECTOMY BY THE TRANSTHORACIC APPROACH

REPORT OF SEVEN CASES

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THE TECHNICAL ADVANTAGES of the transthoracic approach in cases of carcinoma of the stomach or lower esophagus invading the cardia are now well established. There remains, however, the necessity for greater experience with the operation before some of the particular details of the technic can be brought more nearly to a state of perfection. The operation of partial gastrectomy, removing the fundus of the stomach, the cardia, and a portion of the lower esophagus, is now being carried out with satisfactory results in several clinics. Experiences with the total excision of the stomach through the transthoracic route, on the other hand, have been few in number and most disappointing in their results. The operative mortality has been prohibitive. The difficulty in the few reported cases seems to have been with leakage from the suture line of the esophagojejunal anastomosis.[1] This has doubtless been the result of the almost unavoidably great tension on the suture line caused by pulling the jejunum up to such a high level.

The physical variation in patients accounts for the fact that in a few the proximal jejunal loop can be brought up to a level an inch or more above the diaphragm without excessive tension, whereas in the majority the mesentery of this loop is too short. In two of the seven cases reported in this article it was possible to pull the upper jejunal loop high enough to perform an anastomosis slightly above the level of the diaphragm without an intolerable degree of tension. In the other five cases, although the loop could be brought to the level of the diaphragm in three of them, the level of invasion of the lower thoracic esophagus was so high that in order to cut well above the upper limit of the tumor it was necessary to transect at a level which was two to three inches above the highest point to which the jejunum could be drawn even under tension. It was the necessity for overcoming this difficulty which led to the development of the technic which is to be suggested here.

In 1942, the first report of a successful total gastrectomy using the transthoracic approach was made by Willy Meyer.[2] In this case there was great tension on the suture line and, as a result, a jejunal fistula developed which discharged through the chest drainage tube. This fistula eventually closed spontaneously, and the patient recovered. Although the level at which the esophagus was cut across is not stated exactly, one might assume from the description that the anastomosis was not unusually high above the diaphragm. This was true of the first successful case in the Massachusetts General Hospital series. In three of the others, however,

the end of the esophagus and the apex of the jejunal loop could not be brought within two or three inches of each other.

The fundamental principles of freedom from excessive tension on the suture line, and adequate preservation of blood supply to the parts, must be observed in this as in all other portions of the field of gastro-intestinal surgery. In any anastomosis involving the esophagus a careful layer-by-layer approximation of the cut edges must likewise be observed. As was pointed out formerly,[3] the lack of a serosal layer in the esophagus alters

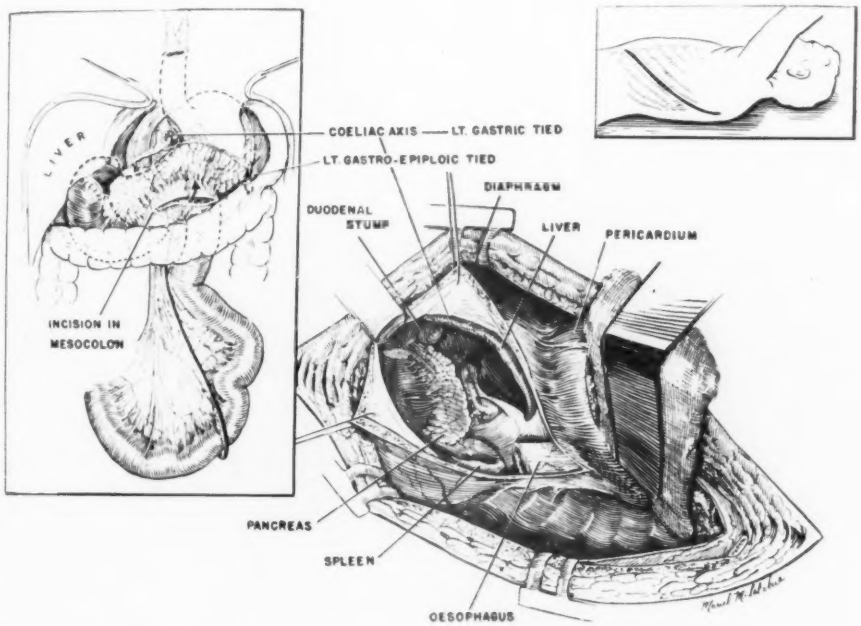

FIG. 1.—General view of the field of operation after the stomach has been removed showing the lung retracted, the edges of the diaphragm parted, the duodenal stump sutured, and the cut end of esophagus ready for the anastomosis. Insert upper right shows the direction of the incision over the ninth rib on the left side. Insert to the left shows the level of transection of the esophagus above the diaphragm, the line of incision in the transverse mesocolon, and the proximal loop of jejunum which is to be used for the anastomosis. Note the vascular pattern in the mesentery of this loop.

the pattern of healing in such suture lines and great stress must be laid on an accurate suture of the mucosa which in the esophagus holds sutures better than the muscularis. This is to be accomplished best by means of a layer of fine silk placed in such a manner that the knots are tied on the side of the lumen. In the approximation of the muscular layer mattress sutures of fine silk give satisfaction with less tendency to tear out than common single sutures.

OPERATIVE TECHNIC TO AVOID TENSION IN ESOPHAGOJEJUNOSTOMY

On being confronted with the problem of performing an esophagojejunal anastomosis in a case where the two organs cannot be brought together by ordinary means, one's first impulse is to use the Roux procedure. The chief objections to this are, first, the danger of damage to

the vessels of the divided jejunal mesentery, and, secondly, the fact that an end-to-end anastomosis using the esophagus presents technical difficulties which are likely to compromise the result. The difficulty may be overcome as follows:

The usual transthoracic approach through the bed of the ninth rib is made. After removal of the entire stomach and closure of the duodenal stump, an opening should be made in the transverse mesocolon at a

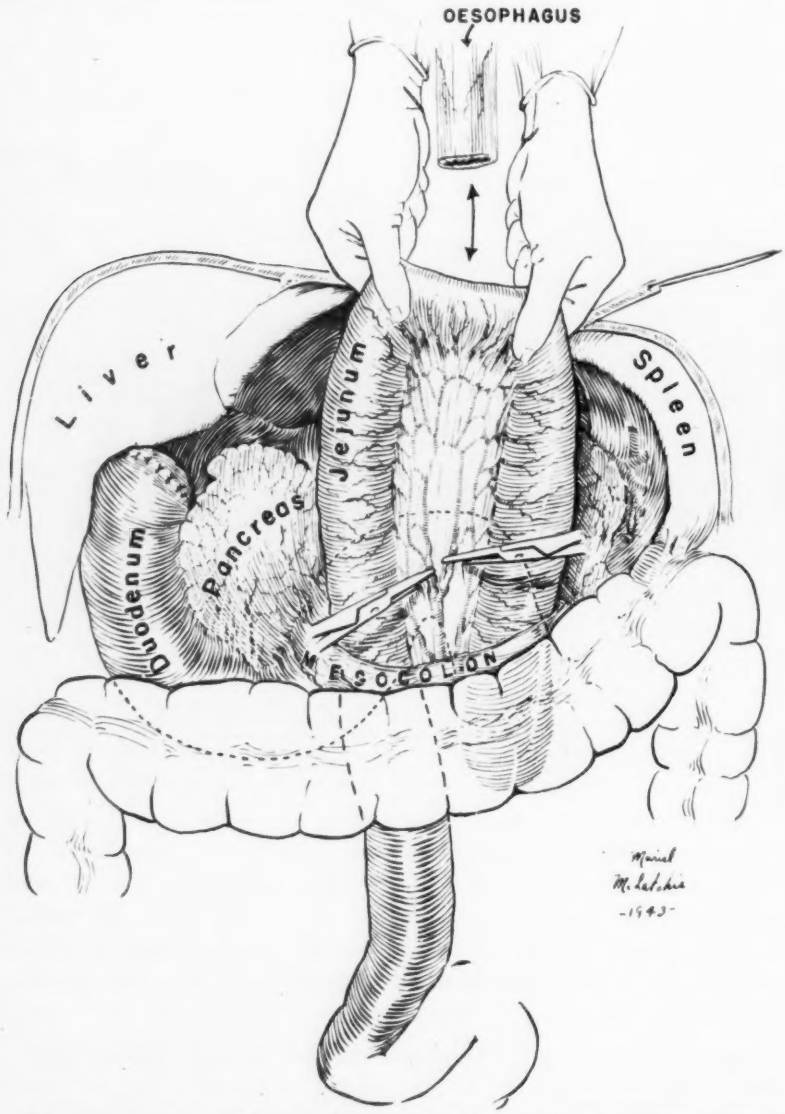

FIG. 2.—Proximal loop of jejunum drawn up through the transverse mesocolon. The pull of the mesenteric vessels makes it impossible to extend the apex of the loop much above the level of the diaphragm. Anastomosis with the esophagus not possible without release of the pull of the mesenteric vessels. Point of division of these vessels shown by hemostatic forceps in the drawing.

convenient point, taking care to avoid the middle colic vessels (Fig. 1). The highest jejunal loop is then drawn up through the mesocolon, and in the majority of cases can be pulled no further than one or two centimeters above the level of the diaphragm (Fig. 2). In every case the reason for

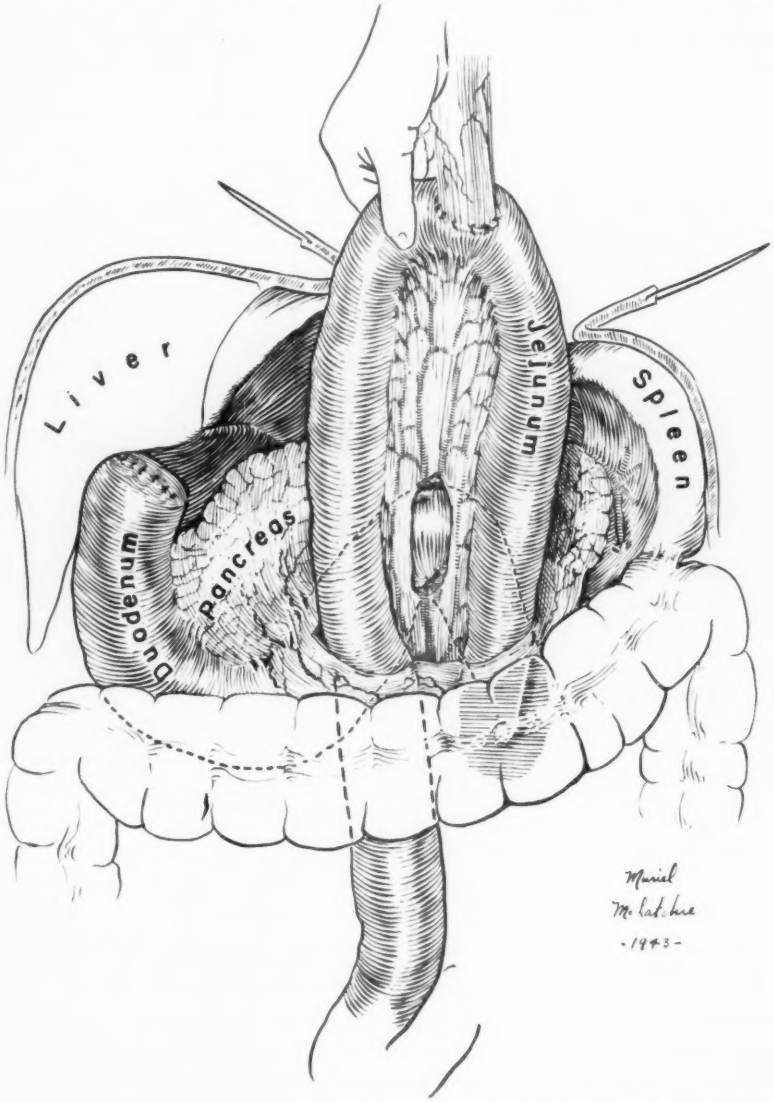

FIG. 3.—Marked release of tension after division of the mesenteric vessels makes it possible to bring the proximal loop of jejunum high above the diaphragm into the chest, and the esophagojejunostomy is performed without tension on its suture line.

this is that the vessels of the mesentery are too short to allow the loop to go beyond that point although the bowel itself, if freed from the pull of the mesenteric structures, can be drawn up to any level. In some cases a slight amount of relaxation of the pull results from dividing the ligament

of Treitz. This is rarely sufficient to make an appreciable difference. If, however, the main artery which supplies the proximal jejunal loop is sought out and cut between ties close to its origin from the superior mesenteric artery, and if the vein is treated likewise, the pull of the mesentery on the loop is greatly relaxed and its apex can be advanced as much as three inches into the chest above the level of the diaphragm (Figs. 2 and 3). Great care must be exerted to avoid damage to the

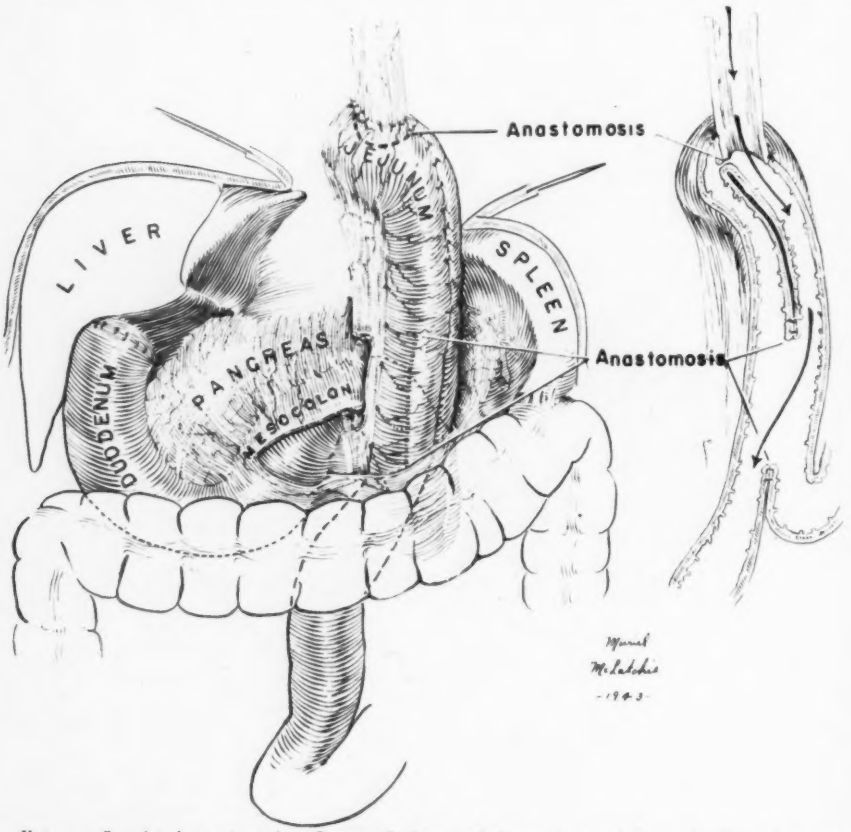

FIG. 4.—Completed anastomosis. Roscoe Graham technic used to reinforce the line of suture. Entero-enterostomy between the afferent and efferent arms of the jejunal loop shown just above the level of the opening in the transverse mesocolon. Insert shows vertical section of lower esophagus and jejunal loop to which it has been anastomosed—entero-enterostomy shown.

collateral vascular arches during the division of the primary vessels and to avoid tearing or overstretching them as the loop is pulled up after division.

When the pull of the mesentery on the proximal jejunal loop has been relaxed by this means, the anastomosis can then be carried out without danger of its pulling apart later because of too much tension.

The exact technical details of the anastomosis may be varied to suit the indications of the individual case and the personal preference of the surgeon. I have used the Roscoe Graham method with great satisfaction.[4] By this means a desirable extra reinforcement of the suture line is

easily obtained (Fig. 4). It makes no difference whether the proximal (afferent) arm of the loop is used to wrap around the line of anastomosis or the distal (efferent) arm, providing an entero-enterostomy is carried out between the two arms of the loop, as Graham recommends. It is important that the loop of jejunum be brought up in such a way that the afferent arm shall be short enough so as not to sag down below the level of the entero-enterostomy. In this way puddling of food in the proximal arm and in the duodenum can be avoided. It is not necessary to suture the divided jejunal mesentery or the opening in the transverse mesocolon.

After the anastomoses are completed the jejunal loop must be anchored by means of sutures to the mediastinal pleura and to the cut edges of the diaphragm as they are brought around it. The remainder of the diaphragm is then closed with interrupted silk sutures and motion is minimized by crushing the left phrenic nerve within the thorax by means of a hemostatic forcep.

The above method of relaxation of the jejunal mesentery followed by an anastomosis using the Roscoe Graham method was employed with complete satisfaction in three of the seven cases reported. Without it, in these cases, no anastomosis could have been carried out excepting possibly a modification of the Roux procedure.

The operation of total gastrectomy followed by an esophagojejunal anastomosis has been performed seven times at the Massachusetts General Hospital. In all, the choice of the transthoracic approach resulted from the fact that the tumor was close to, or had actually invaded, the cardia and in some of the cases the lower esophagus as well. The decision to remove the entire stomach was made on the basis of the widespread involvement of the organ. Two patients died postoperatively, both of sepsis. In the first of these the death may be said to have resulted from a technical error because the suture line was found at autopsy examination to have separated in part. If the procedure of dividing the vessels at the base of the proximal jejunal loop so as to relax the tension on the suture line had been followed in this case, there is reason to believe that the fatal result could have been avoided. The widespread infection which was the cause of the death of the second patient could hardly have been avoided in the present state of our knowledge. This patient was in a seriously debilitated condition resulting from obstruction at the cardia by a recurrent carcinoma of the stomach following a partial gastrectomy with a posterior Pólya anastomosis. In this case there was more opportunity for soiling to occur than in the average because of the necessity of undoing the previous anastomosis. At autopsy there was peritonitis and empyema, but the esophagojejunal anastomotic suture line was intact.

Each of the remaining five patients recovered promptly without major complications. In the first two of these there was no difficulty in pulling

the proximal jejunum up to the level of division of the esophagus, which was not high. In the last three cases it was necessary to divide the esophagus at a relatively high level. In each of these cases it was impossible to bring the eophagus and jejunum together before the jejunal mesenteric vessels had been divided. In the last case the proximal loop could not be used at all because of extensive adhesions resulting from a former widespread acute peritonitis. In this instance it was necessary to use the next lower jejunal loop, and by dividing the vessels at the base of its mesentery it was possible to pull it well up above the level of the diaphragm into the thorax.

REPORT OF SEVEN CASES

Case 1.—M. G. H. No. 294086: M. O., female, age 55, entered the Massachusetts General Hospital March 21, 1941. She had had vomiting and weakness for the past year, and gradually increasing difficulty in swallowing. In the attempt to relieve her various forms of treatment had been carried out, including cholecystectomy three months prior to admission.

Examination showed a pale, ill-nourished woman. Her blood chemistry was essentially normal, and her Hinton negative. Roentgenologic examination showed a carcinoma of the lower third of the esophagus extending to the mid-portion of the body of the stomach. There were no visible metastases in the chest. Esophagoscopy showed no positive evidence of neoplasm and biopsy was unsatisfactory. Three centimeters above the cardia the mucosa looked red, and there were white plaques.

Operation.—April 2, 1941: A transthoracic total gastrectomy with esophagojejunostomy, splenectomy, and partial pancreatectomy was performed. Under intratracheal gas-oxygen-ether anesthesia, the patient was placed on her side and an incision made along the entire length of the tenth rib on the left, which was exposed and resected subperiosteally. This rib was chosen because it was partly floating and probably, therefore, not the lower fixed point of the thoracic cage. The left lung was found free, was retracted upward, and the esophageal hiatus exposed. The phrenic nerve was paralyzed by crushing it as it crossed the pericardium, and the diaphragm was then opened in the direction of its fibers from the esophageal hiatus laterally. This exposed the spleen and stomach. Exploration revealed no evidence of liver metastases. The pelvis was free. Within the fundus of the stomach there was a large, hard tumor mass which extended into the lower inch of the esophagus. There were numerous firm nodes along the left gastric vessels. The esophagus was freed-up above the tumor and a tape passed around it. The vasa brevia were clamped, cut, and ligated and the lesser omental bursa thus exposed and explored. The growth seemed resectable and dissection was, therefore, begun along the lateral aspect of the stomach. The peritoneum was reflected medially and numerous nodes were found near the splenic pedicle. The omentum was now opened along the greater curvature and a generous segment of it excised. Dissection was carried towards the pylorus which was finally freed on both sides and then cut across between Kocher clamps just on the duodenal side. The stomach was reflected medially, separating the attachments of the gastrohepatic ligament, until it was entirely mobilized down to the left gastric pedicle. It then seemed wiser to undertake a block resection of the tip of the pancreas, spleen, and left gastric pedicle, and this was carried out without difficulty, thus freeing the entire stomach to the esophagus. The esophagus was transected above the growth. The duodenal stump was inverted with a running atraumatic suture reinforced with interrupted silk, and the jejunum identified at the ligament of Treitz and a loop brought up through a rent in the transverse mesocolon. This was barely long enough to

reach the cut end of the esophagus. A little more length was secured by partially cutting the ligament of Treitz. A careful esophagojejunal anastomosis was performed, using many interrupted silk sutures in two layers, one mucosal and one muscular, with numerous sutures posteriorly to suspend the jejunum to the crura of the diaphragm. There was edema of the medial side of the esophagus through which the stitches tore, and this portion of the anastomosis was not completely satisfactory for this reason. An entero-enterostomy was performed between the two layers of jejunum and brought to lie just below the opening in the transverse mesocolon, which was loosely closed around them. A leaf of omentum was brought up to cover the jejunum and the region of the anastomosis, and the diaphragm reapproximated in two layers around it. A catheter, for drainage of the chest, was brought in through the next lower interspace posteriorly, and the chest wound closed in layers.

Pathologic examination showed the specimen to contain carcinoma of the stomach, with extension to the pancreas and esophagus, and metastases to the regional lymph nodes.

The patient had a severe febrile reaction following the operation. Her chest was aspirated on several occasions, and bloody, foul-smelling fluid obtained. There was drainage from her chest tube, at first thick and small in amount, then thin and copious, resembling the large return from her nasal tube. Roentgenograms showed a combination of fluid and atelectasis on the left side. She was treated by means of sodium sulfapyridine and transfusions, but continued to go downhill and died, nine days after operation. At autopsy, she was found to have empyema and pericarditis resulting from almost complete separation of the anastomotic suture line.

Case 2.—M. G. H. No. 132669: G. W., male, age 46, entered the Massachusetts General Hospital September 17, 1941. Three years before entry he had had a subtotal gastrectomy for what had been thought to be gastric ulcer, but pathologic examination of the specimen proved it to be carcinoma. For the past five months he had had increasing dysphagia with marked loss of weight. Gastro-intestinal series five days before admission showed no evidence of obstruction or metastasis in the esophagus, stomach, or in the anastomosis. Twenty-four hours prior to admission he had developed generalized periumbilical and lower abdominal pain, with nausea but no vomiting. The pain localized in the right lower quadrant and he was sent to the hospital.

Examination showed the patient to be a thin but well-developed man, with several small hard nodes in the left supraclavicular fossa. The chest and heart were negative. There was the sensation of a mass, in the right upper quadrant, and a question of spasm. There was slight spasm but no mass in the right lower quadrant, with localized tenderness about McBurney's point. Rectal examination showed fairly acute tenderness and fullness on the right.

A diagnosis of acute appendicitis was made, and the patient was operated upon. A perforated appendix was found. His convalescence was uneventful except for extensive infection of the wound.

Laboratory studies of his blood showed 3.45 red cells, 12,600 white cells, and a hemoglobin of 70 per cent on admission.

Thirteen days after appendicectomy roentgenologic examination of the esophagus showed what was interpreted as either cardiospasm or extrinsic pressure just above the hiatus. Subsequent roentgenograms revealed a mass involving the lower end of the esophagus, as well as the medial aspect of the fundus of the stomach, with the greater portion of the mass apparently outside the mucosa. These findings were interpreted as being due to recurrent carcinoma.

Esophagoscopy was performed October 6, 1941. There was a small amount of brownish, granular material in the lumen which was readily sponged away. The mucosa throughout the esophagus showed slightly enlarged rugae and seemed a little

redder than normal, but hardly enough to make a diagnosis of esophagitis. Bougies sizes No. 12 to 22 passed readily through the cardia into the stomach. Examination was essentially negative, and it was felt that if the symptoms persisted, it might be wise to use the mercury bougie.

First Operation.—It was decided that exploratory celiotomy was indicated, and this was undertaken October 18, 1941. A vertical left rectus incision was made, and through this the abdomen was explored. There was found to be apparently a mass of malignant disease in the lymph nodes around the left gastric vessels. It seemed to be loosely attached to the posterior tissues. The portion of the stomach which was left after the gastric resection was wrapped over the tumor, which had pushed from the medial side into the region of the cardia, where it produced a crescentic slit-like opening into which it was impossible to push the finger through the anterior stomach wall. The region of the gastrojejunostomy appeared to be perfectly smooth, and there was no evidence of disease anywhere except as described. The liver seemed to be free from metastases. A jejunostomy was performed, taking care to leave a long proximal loop in case an excision should be undertaken through the lower part of the chest. The patient's course following exploration and jejunostomy was uneventful. He was comfortable and gained strength rapidly.

Second Operation.—November 4, 1941: A transthoracic total gastrectomy and splenectomy were performed. A long oblique incision was made over the 9th rib on the left side. The entire length of the 9th rib was resected. The chest was opened. There were no adhesions, no fluid, and no evidence of pulmonary metastases. The diaphragm was then incised and the tumor was explored. It was essentially the same as previously noted, but it was soon discovered that the adhesions posteriorly were very dense. After considerable dissection it was finally decided that it could be removed. The operation was then proceeded with and, in order to get good access to the posterior attachment, the esophagus was divided early in the procedure. The stomach was then turned down and much of the posterior attachment in the region of the left gastric vessels was freed. The left gastric vessels were freed and the transverse mesocolon removed from its attachment to the stomach. The anastomosis was opened by cutting along the suture line and the cut end of the stomach inverted to prevent gross soiling during the manipulation of delivering the mass. The opening in the jejunum was sutured transversely with two layers of chromic catgut reinforced with several silk sutures. The tumor mass along with the entire remains of the stomach was then removed by cutting posteriorly, and in doing this a section of the pancreas had to be removed along with a portion of the splenic artery. The vessels were tied and the spleen was then quickly removed because of its lack of blood supply. At this point, considerable bleeding was noticed and the stump of the splenic artery was immediately exposed and found to be bleeding because the tie had come off. It was quickly secured and carefully tied with a heavy silk ligature. An end-to-side anastomosis was then performed between the apex of the jejunal loop above the jejunostomy and the cut end of the esophagus. The incision in the jejunum was placed transversely across the length of the bowel and the loop was wrapped around the lower end of the esophagus, after the Roscoe Graham method. An entero-enterostomy was established between the two arms of the jejunal loop. Some omentum was brought up and the loop was held up by attaching the leaves of the pulmonary ligament to it. The diaphragm was then closed, but care was taken to avoid constriction. It was sutured in several places to the two arms of the jejunal loop. The phrenic nerve was crushed, and the chest closed without drainage. Eight Gm. of sulfanilamide were distributed in the upper abdomen and lower part of the left hemithorax.

Pathologic examination of the specimen removed was reported as adenocarcinoma of the stomach, recurrent in the wall of the lower esophagus.

Postoperative Course.—Following resection, the patient made an excellent immediate recovery, but on the third day an aspiration of the left side of his chest yielded 700 cc. of serosanguineous fluid. A culture of this showed abundant growth of *B. coli* and nonhemolytic streptocci. On the fifth postoperative day it was apparent that he had fluid at his right base and there was also evidence of pneumonia in the right lung. He did not develop much elevation of temperature, but it was apparent that he was losing ground. Two days after this he suddenly became dyspneic. Seven hundred cubic centimeters of purulent fluid were removed from the left side of his chest. He was placed immediately in an oxygen tent, but died suddenly the same afternoon. Autopsy revealed that there was pus in the upper part of his abdomen, in the left side of his chest, and also an empyema on the right side, with evidence of bronchopneumonia in both lungs. The suture line was intact and there was no evidence of any leakage.

The presumption is that this patient, already depleted by long-standing starvation and the presence of a large carcinoma, did not have sufficient resistance to withstand the infection which resulted from the soiling of the field at the time of operation.

Case 3.—M. G. H. No. 361509: M. K., male, age 56, was admitted to the Massachusetts General Hospital, June 27, 1942, complaining of anorexia and abdominal pain. Three years before admission he had had a strangulated right inguinal hernia repaired. The hernia recurred one month later, and at that time he began to have symptoms of low-grade intestinal obstruction with cramps, "gas pains," rare vomiting, and occasional diarrhea. Two years before admission he had been operated upon after roentgenologic examination of the gastro-intestinal tract showed a mass in the large intestine. The abdomen was explored, and a large, apparently inoperable carcinoma of the stomach, located on the lesser curvature and extending almost to the esophagus, had been found. This involved the entire lesser curvature, according to the surgeon, and had metastasized to the aortic nodes, the sigmoid, and the bladder region. The prognosis was considered hopeless and no further operative procedure was attempted.

He remained in the hospital for seven months following the exploratory celiotomy, and at discharge weighed 120 pounds. Since that time he had remained in much the same condition, with poor appetite, constipation, gas and borborygmus. His diet consisted of milk and eggs. He complained of knife-like periumbilical pain coming on usually 15 minutes after eating and persisting for hours or days. On the other hand, he had gone as long as a week without distress. He had gained about 30 pounds in the past year and a half, but was too weak to do anything but very light work. He had had no vomiting, no nausea, and had never noticed blood in the stools. He was almost always conscious, however, of gas and intestinal rumbling. He remained obstinately constipated and required large doses of mineral oil. He had noticed recently that his ankles were swelling after he had been up for some hours. He had no urinary symptoms other than nocturia.

Because of the persistence of his symptoms the patient reported to the Massachusetts General Hospital Out-patient Clinic. A gastro-intestinal series was advised, and when fluoroscopy revealed dilated loops of small bowel he was admitted to the hospital at once and a Miller-Abbott tube passed.

Physical examination revealed a well-developed, poorly nourished, apathetic, middle-aged male. The heart was normal. Blood pressure 105/60. The chest was negative. The abdomen was flat. Peristalsis was active. The liver and spleen were not felt. Rectal examination was negative.

Roentgenologic examination before admission showed markedly dilated loops of small intestine. Fluoroscopic examination of the abdomen four hours after the motor

meal had been given showed the dilated loops to be probably mid- and lower-jejunum. The obstruction could not be outlined because of insufficient filling of the loop, which was dilated and contained a considerable amount of fluid in addition to the small amount of barium. It was thought that the obstruction was near the pelvic brim, and the patient was slightly tender in this area on palpation. A barium enema showed inadequate filling of the midsigmoid but gave no other definite information.

Laboratory studies showed the patient to have a hypochromic anemia, with a red blood cell count of 3.32; white count of 11,600; and photohemoglobin of 6.1 Gm. The differential showed 55 polymorphonuclear cells, 8 large lymphocytes, 28 small lymphocytes, 7 monocytes, 1 basophil, and 1 young polymorphonuclear cell. The serum protein was 3.5 per cent, the chloride 105.9 mg. per cent, nonprotein nitrogen 23 mg. per cent, and the CO_2 combining power 24.1 mg. per cent. Uranalysis showed albumin +++, with 20 to 30 hyaline or granular casts per high power field, and 5 to 10 white blood cells.

First Operation.—July 2, 1942: A resection of the terminal ileum, with entero-enterostomy and resection of the sigmoid, with colostomy were performed. The abdomen was opened through a right paramedian incision. The upper three-fourths of the small intestinal tract was normal in appearance. The lower fourth was a matted mass of bowel, greatly dilated and fibrosed. It was adherent in the left lower quadrant to the sigmoid and bladder. Distal to this point, which was about six inches proximal to the ileocecal valve, the ileum was collapsed. The large bowel was normal otherwise. Palpation of the stomach revealed a very large carcinoma of the fundus, which was freely movable and did not appear to involve the esophagus. There were a few small, hard, nodules in the liver, one of which was removed for biopsy. The bowel was dissected free from the sigmoid and a fistulous opening was found to exist between the two. There was some tissue in the sigmoid which suggested malignant disease.

The large matted mass of intestines was resected. Six inches of the terminal ileum were saved. The end of this and the distal end of the upper ileum were turned in with running catgut for mucosal sutures and interrupted Halsted mattress sutures of cotton. A side-to-side anastomosis was performed between the two portions of ileum, using two layers of running catgut sutures. The proximal end of the anastomosis lay inferior to the distal end. The Miller-Abbott tube had descended to this level and the tip of it was passed through anastomosis.

Because of the opening in the sigmoid and the question of malignant disease in it, this was resected and the cut ends brought out through a McBurney incision in the left side of the abdomen. The loops were not sutured together as it was intended to reanastomose them by an end-to-end suture after resection of the stomach. The abdomen was closed in layers, after sprinkling the peritoneum with sulfanilamide powder.

Pathologic examination of the specimens removed showed a 1 x 0.5 x 0.2 cm. fragment of liver which was almost completely replaced by white, glistening friable tissue. This proved to be metastatic adenocarcinoma. There were approximately two feet of ileum which was thrown into six knuckles, firmly bound to each other by dense bands of old fibrous tissue. In one place these adhesions formed a slightly elevated gray plaque, measuring 1 x 2 cm. At this point the wall had an average thickness of four millimeters. Elsewhere the average thickness was two millimeters. The mucosa was negative. Also submitted was a portion of large bowel, measuring eight centimeters, which was grossly negative. A diagnosis of intestinal obstruction due to adhesive bands was made.

Postoperative Course.—The patient did well following operation until the 17th day, when both legs were found to be swollen about the ankles. Ten days later he had a slight fever lasting for two days, and complained of some pain in his right

chest. Roentgenologic examination of the chest showed scarring in the right lung, and old pleurisy, consistent with healing infarcts. Because of this and especially because of his prospective long stay in bed, it was felt that this patient should have ligation of both superficial femoral veins. This procedure was carried out on August 2, 1942.

Barium examination of the esophagus and stomach, on August 5, 1942, failed to reveal any pathology. There was considerable food in the stomach. The duodenum was large throughout its length. The first two loops of jejunum were not dilated. No further examination was made.

Second Operation.—August 11, 1942: Transthoracic total gastrectomy and splenectomy were performed, with esophagojejunostomy and entero-enterostomy. Under intratracheal ether anesthesia, the ninth left rib was resected. The lung collapsed satisfactorily on opening the pleura. The diaphragm was then opened and it was ascertained that the lesion was resectable. The left phrenic nerve was then crushed. A gastrectomy was performed removing one and one-half inches of esophagus, the lower end of which was involved in the carcinoma. The diaphragm was then severed in its entirety, leaving about one centimeter around the esophageal hiatus. This was done in order to use this portion of the diaphragm as a support for the jejunum, as it was found impossible to bring the jejunum within the thorax without undue tension. An end-to-side anastomosis was performed after freeing up the esophagus and bringing it down through the esophageal hiatus. Three rows of interrupted cotton mattress sutures were used. The outer layer was between the diaphragm and jejunum; the inner two layers were between the esophagus and jejunum. There were very few if any metastatic nodes to be noted. A few small metastatic nodules were palpable in the liver. As the spleen was in the way of the stomach it also was resected along with a portion of the pancreas. An entero-enterostomy was performed between the distal and proximal jejunal loops, as there seemed to be a little kinking of the distal jejunal loop where it was sutured to the diaphragm. The diaphragm was then closed with interrupted cotton and a running catgut suture. The chest wall was closed in layers. A whistle-tip catheter was brought out through the ninth interspace. Sulfanilamide was used around the anastomosis and in the thoracic wound.

Pathologic Examination.—Gross: The specimen showed a totally resected stomach including 1 cm. of esophagus and 2 cm. of duodenum. It measured 18 cm. in length and 14 cm. in circumference. It contained in its center a large, indurated, fungating, partially annular neoplasm measuring 10 cm. in length, 16 cm. in circumference and 5 cm. in thickness. The serosa was smooth but moderately elevated over the nodular, firm, external surface of the lesion. The mucosa was smooth, pale, and pebbly except for the neoplastic area where there were hard fungating nodules measuring up to 3 cm. in maximum diameter protruding up to 2 cm. above the surface. There were some superficial necrotic areas. No lymph nodes were attached to the specimen, but a separately submitted lymph node was firm, gray, and measured 8 mm. in diameter. *Pathologic Diagnosis:* Adenocarcinoma of the stomach.

The patient's recovery from operation was uneventful, and his subsequent progress excellent. On September 5th the colostomy was closed and he was discharged 18 days later, six weeks after the gastrectomy. On December 6th, four months after the gastrectomy, he was in only fair condition and probably beginning to fail because of the metastatic disease in the liver.

Case 4.—M. G. H. No. 68281: B. S., female, age 59, was admitted to the Massachusetts General Hospital on December 14, 1942. She had had two previous admissions, one in 1937 for removal of a left temporal meningioma and the second in 1941 for ligation of the left saphenous vein. Her complaint at this time was of increasingly severe anorexia for the past six or seven months accompanied by weight loss of approxi-

mately 30 pounds. Because of this she had gradually eaten less and less and, for the past few weeks, had taken nothing except milk. During the past two months she had had epigastric pain which radiated around the right side to the back. Associated with this pain, which was unrelated to meals or to the type of food eaten, was a feeling of fullness in the abdomen, particularly in the epigastrium. She had been nauseated but had vomited only one or twice. There had been no hematemesis. There had been no change in bowel habit and no tarry or bloody stools. She had had no cough, chest pain, or hemoptysis. She had had a gradually increasing feeling of weakness associated with some dyspnea on exertion. There was a history of cancer in a number of members of her family.

Physical examination showed a middle-aged, pale woman, with evidence of recent weight loss. There were a few small nodes in the left axilla. There were no supraclavicular nodes. The heart was enlarged by percussion 1.5 cm. outside the midclavicular line. There was slight splitting of the first sound at the apex with faint, soft systolic murmur and an occasional extra systole. Blood pressure 140/60. The lungs were clear. Abdominal examination showed a relaxed and flabby abdominal wall with numerous striae. The liver was palpable on deep inspiration about two fingers breadth below the costal margin. It was smooth and not tender. There was no palpable mass.

Laboratory studies showed a white blood cell count of 6700; a red count of 5.80, and hemoglobin of 100 per cent. Stool was guaiac-negative. Gastric analysis before histamine revealed guaiac ++++ reaction, free acid 0, combined acid 16; after histamine, analysis of 1.5 oz. of mucoid, grossly bloody fluid showed no free acid, combined acid 34, total acid 34. Serum protein 6.0 mg. per cent.

Roentgenologic examination of the esophagus was not remarkable. The lumen of the stomach, however, was markedly decreased in size. The stomach wall was thickened and the mucosa was destroyed from the fundus to a point about six centimeters proximal to the pylorus. The duodenum and upper jejunum were not remarkable. The appearance was that of scirrhus carcinoma. There was no definite evidence of involvement of the lower esophagus. Examination of the dorsal and lumbar spine was negative. The lungs were clear and the heart not remarkable.

Operation.—December 23, 1942: A transthoracic total gastrectomy with esophagojejunostomy, splenectomy, and entero-enterostomy was performed. A long incision was made over the course of the 9th rib on the left side, and the 9th rib was resected. The lower lobe of the lung was quite adherent and had to be freed so as to get at the diaphragm. The diaphragm was divided after first paralyzing the phrenic nerve with novocain. The stomach was explored and it was found that it could be brought up easily. There were no adhesions and there was no invasion of any adjacent structure excepting the hilum of the spleen where the growth had apparently begun to extend. This made it necessary to remove the spleen along with the stomach. The major portion of the stomach was involved so that a total gastrectomy was the only logical procedure.

The diaphragm was divided completely through the hiatus. The phrenic nerve was crushed and the stomach was freed by cutting the diaphragmatic attachments and the left gastric vessels. The spleen was then removed, tying the artery and vein separately, and the incision was carried between the spleen and the pancreas and along the gastrocolic ligament. At this point, it seemed to be easier to cut across the esophagus and turn the stomach up so as to get access to the duodenum. This was, therefore, done, using Dr. Smithwick's special clamp and closing the end temporarily with a basting-stitch of silk. The duodenum was then freed. An attempt was made to tie it, but the tie slipped off and it then became necessary to invert it in the usual way, using a Connell suture on the inner layer, a second layer of running

Lembert stitch, and an outer layer of Lembert mattress sutures, using interrupted silk.

The upper loop of jejunum was then brought out. It had a very short mesentery so that it was impossible to bring the loop very high into the chest. A satisfactory anastomosis was made, however, using the end of the esophagus to the side of the jejunum with two layers of interrupted silk sutures, an inner layer in mucous membrane and an outer layer of mattress sutures in the muscularis.

An entero-enterostomy was performed between the two arms of the jejunal loop using two layers of sutures, catgut inside and fine silk on the serosal side. In doing this it seemed wise to fold the jejunum over and wrap it around the anastomosis and esophagus, in very much the same way as advocated by Roscoe Graham. This was done using silk sutures. The jejunal loop all around to the anastomosis was firmly fixed to the posterior cut edges of the diaphragm with interrupted silk sutures. A portion of omentum was brought up and fixed around the anterior part of the anastomosis. A stomach tube was then threaded down through the esophagojejunostomy into the proximal arm of the loop and down through the entero-enterostomy into the distal arm. This route was chosen because it seemed to be the most direct.

About six Gm. of sulfanilamide was introduced, some in the upper abdomen and some in the chest. The diaphragm was closed with interrupted silk sutures and, after putting a catheter in the interspace below, the chest was closed in layers in the usual way. The lung was thoroughly reexpanded before chest closure was made.

Pathologic Examination.—The specimen showed a complete stomach to which was attached a 300-Gm. normal-appearing spleen. The stomach measured 15 cm. on the lesser curvature and 20 cm. on the greater curvature. The wall was 7 mm. thick in the area of the tumor, which occupied the proximal 10 cm. of the specimen. The tumor stopped abruptly in the distal third and here the mucosa was intact, normal in appearance, with walls less than 5 mm. thick. The serosa over the tumor-bearing area was red and brawny, elsewhere smooth and shiny. Dense tissue seemed to be growing into the fat at the lesser curvature. One soft lymph node was found. *Pathologic Diagnosis:* Scirrhus carcinoma and arteriosclerosis of the spleen.

The patient's postoperative convalescence was comfortable and complicated only by thrombophlebitis occurring on the 22nd day after operation, because of which the left superficial femoral vein was ligated and jelly-like clot removed both distally and proximally.

Case 5.—M. G. H. No. 387483: W. S., male, age 49, entered the Massachusetts General Hospital, December 31, 1942, having been referred by his local doctor with a diagnosis of inoperable carcinoma of the stomach. About one and one-half years previously the patient had been studied elsewhere because of severe hematemesis, and had been told that he had ulcers of the stomach. He had been treated medically, with apparently satisfactory remission of his symptoms. About four months before admission, however, because of vague digestive disturbances and vomiting, a roentgenologic examination resulted in a diagnosis of carcinoma of the stomach being made. He had had no more hematemesis. An exploratory celiotomy had been performed, and an apparently inoperable growth found. The carcinoma was large, was located at the very upper end of the lesser curvature and appeared to extend into the lower esophagus, with posterior extension of the lesion. Following the operation the patient had felt poorly, had lost about 30 pounds in weight, had vomited almost everything he had eaten, and had had increasing difficulty in swallowing. He had had a little abdominal pain, but his main problem was that of starvation. He complained of increasing constipation, but had had no melena or bloody stools. He had always been well up to the time of his present illness.

Physical Examination.—The patient was a pale, somewhat cachectic white male, showing evidence of chronic wasting disease. There were almond-sized bilateral, non-

tender inguinal nodes and shotty epitrochlear nodes. The chest was emphysematous, the diaphragms low, and the costal margins flared. The abdomen was scaphoid. There was a well-healed, recent, nontender, right upper midrectus scar. The liver margin was soft and not tender at the right costal margin. In the right epigastrium there was a deeply felt, nontender resistance, with a questionable mass.

Roentgenologic examination of the gastro-intestinal tract showed a defect in the lower end of the esophagus extending from the cardia and continuing around the

FIG. 5.—Case 5: Preoperative roentgenogram of stomach showing large filling defect involving lower esophagus, cardia, fundus, and proximal two-thirds of lesser curvature of stomach.

stomach in an annular fashion. The involvement extended down upon the stomach to the distal third, where free peristalsis began and the stomach wall was quite flexible. The duodenal bulb was normal. There was no great amount of obstruction at the cardia. The findings were those of carcinoma of the cardia involving the lower end of the esophagus and adjacent stomach (Fig. 5). Examination of the chest showed no evidence of metastases.

Laboratory studies showed the white blood cells 4000, the red cells 4.18, hemo-

globin 100 per cent. Examination of the stools gave a positive guaiac test. The vomitus showed a negative guaiac reaction.

Operation.—January 12, 1943: A transthoracic total gastrectomy was performed. A long oblique incision was made along the course of the ninth rib on the left side. The entire ninth rib was resected. There was no fluid in the chest cavity. The lung felt normal. The tumor could be felt through the diaphragm. The diaphragm was opened and the tumor explored. It was a very large carcinoma involving the lower esophagus as far as a point about two inches above the diaphragm and extending down the lesser curvature and posterior wall of the stomach almost to the pylorus. The posterior wall was adherent to the pancreas and it was necessary to remove a small portion of the pancreas along with a loop of the splenic artery. This made it necessary to perform a splenectomy.

The entire stomach and lower esophagus were freed. The duodenum was grasped

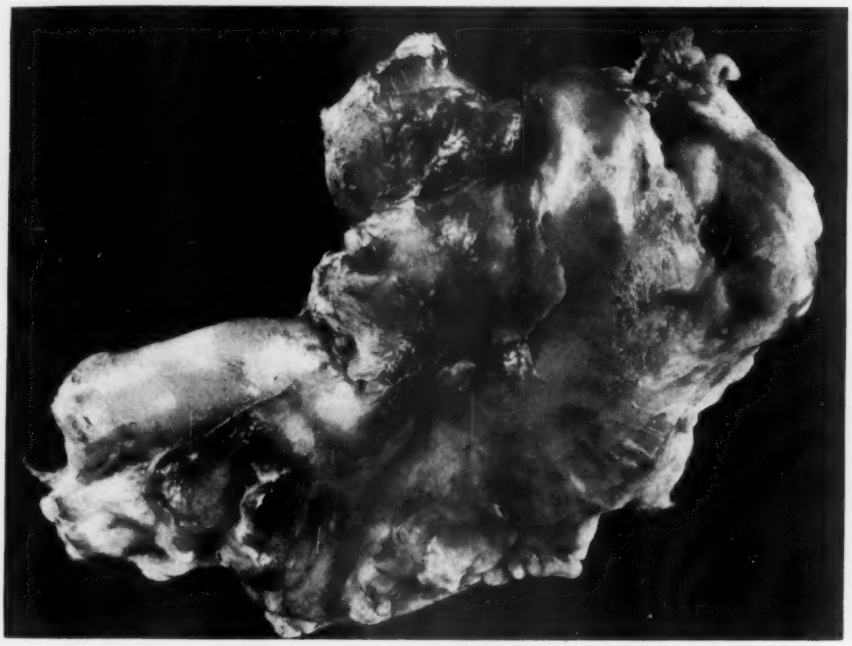

FIG. 6.—Case 5: Photograph of the specimen consisting of the entire stomach, including a portion of lower esophagus.

with the Jones clamp and inverted, using the Jones clamp method. This was accomplished without difficulty and reinforcing sutures were used to hold the pancreas over the inverted duodenal end. The esophagus was then divided at a point about three, or possibly more, inches above the level of the diaphragm. The proximal loop of the jejunum was then brought up through an opening in the transverse mesocolon, and it was found that this loop could not be brought any closer than three or four inches from the cut end of the esophagus. The apex of the loop was barely above the level of the hiatus of the diaphragm. The large vessel at the base of this loop of jejunum was, therefore, divided between two ties, and it was found that this gave enough relaxation of the pull on the loop to allow it to be brought into the chest as far as necessary, and a very comfortable anastomosis, without tension, was made. The jejunal loop was fixed to the edge of the diaphragm posteriorly and to the mediastinal pleura. Anastomosis was made, end-to-side, using three layers, on the

proximal arm of the jejunal loop. The distal arm was then wrapped around, by the Roscoe Graham method, so as to completely cover over the anastomotic suture line. An entero-enterostomy was then performed between the two arms of the jejunal loop. It was found after this was done that the entero-enterostomy lay at a point just above the level of the diaphragm.

FIG. 7.—Case 5: Postoperative roentgenogram showing the wide open esophagojejunal anastomosis several inches above the level of the diaphragm, which is indicated by the constricted appearance of the jejunal loop at that point.

The Levin tube was brought down through the esophagojejunostomy, but it could not be put through the jejunojejunostomy. Silk technic was used throughout excepting for the entero-enterostomy which was done with catgut.

The phrenic nerve was crushed and the diaphragm was sutured around the jejunal loop after covering the entire loop and both anastomoses with a piece of omentum

which came up easily. Suture of the diaphragm was then completed. A catheter was led out through one of the lower interspaces and the wound closed in layers.

Pathologic Examination.—Gross: The specimen consisted of an entire stomach including a portion of the esophagus, measuring 10 cm. on the lesser and 25 cm. on the greater curvature (Fig. 6). On the lesser curvature there was a large, ulcerated, fungating, yellowish-gray, granular, infiltrating mass 11 x 6 x 1 cm. almost completely encircling the cardiac end of the stomach except for an area 2 cm. wide. The mass infiltrated the muscularis of the lower portion of the esophagus and approximately 6 cm. of the lesser curvature. The mass infiltrated the muscle wall and involved the anterior and posterior surfaces of the serosa which was hemorrhagic reddish-brown. Otherwise the mucosa was slightly edematous. No regional lymph nodes were found. Submitted separately was a normal-appearing spleen measuring 12 x 8 x 3.5 cm., weighing 158.5 Gm., and a lymph node measuring 2 x 1 x 1 cm. was also present. The pulp was deep purple and firm. *Pathologic Diagnosis:* Adenocarcinoma of the stomach, acute and chronic gastritis, and moderate arteriosclerosis of the splenic arterioles. The lymph node showed diffuse fibrosis and a considerable amount of brown pigment. This did not take the iron stain, and was probably carbon. There were some foci of multinucleated giant cells which did not resemble those seen in tubercles.

The patient made an uneventful recovery. He was discharged within three weeks of the date of the operation. At that time he was eating a six-meal bland diet with comfort. Postoperative roentgenograms showed a well functioning anastomotic stoma (Fig. 7).

Case 6.—M. G. H. No. 295524, J. C., male, age 54, was admitted to the Baker Memorial, at the Massachusetts General Hospital, December 30, 1942, complaining of substernal discomfort and anorexia. One and one-half years previously he had begun to experience substernal discomfort and tenderness, together with loss of appetite. These symptoms came on suddenly; the patient had always been well although he had never been a very heavy eater. He described his symptoms as a "sick feeling" which came on irregularly, during which time he would feel nauseated but would not vomit, though he would occasionally have regurgitation of a little fluid. These episodes were quite frequent, lasting from 15 to 20 minutes, and were only slightly relieved by soda. They bore no constant relation to meals or exercise and continued up to the time of admission. He had no dysphagia. Shortly after the onset of these symptoms the patient had a gastric series, and three months before his present admission he had had a barium enema, both of which were negative. He had been put on a bland diet after the first roentgenologic examination, but the anorexia had persisted, and during the next six months he had lost 20 pounds. About four months before admission, however, there was a remission in his symptoms, his appetite improved somewhat, and he regained 10 pounds, but for the last three weeks he had had anorexia, again accompanied by a feeling of weakness and fatigue, and he had begun to lose weight again. He thought he noticed dark stools on several occasions, but had had no bloody stools or hematemesis. A week before admission he had had a second gastric series, and as a result of that was advised to be operated upon. His father had died at 79 of cirrhosis and cancer of the liver, but there was no other family history of cancer.

Physical Examination.—The patient was a fairly well-developed and well-nourished man of middle age, pale, but apparently in no distress. His heart was not enlarged. Blood pressure 92/58. There was a soft irregular mass in the left epigastrium, fixed posteriorly, and not tender. The liver edge was not palpable.

Roentgenologic examination of the stomach showed the esophagus to be not remarkable. Just distal to the fundus of the stomach the mucosal pattern appeared altered and in some places destroyed. There appeared to be a small ulceration along

the lesser curvature of the stomach. The stomach appeared to be involved from a point 5 cm. distal to the cardia down to the pylorus. There was no evidence of involvement or of extension through the pylorus. The findings were those of fairly extensive carcinoma of the stomach.

Laboratory studies showed white blood cells 5300, hemoglobin of 14.5 Gm. The stool showed a negative guaiac reaction. Hinton test was negative. Fasting blood protein was 4.7 per cent.

Operation.—January 6, 1943: A transthoracic total gastrectomy was performed, with splenectomy and esophagojejunostomy and jejunal entero-enterostomy. A long oblique incision was made over the course of the ninth rib on the left. The entire ninth rib was resected and the chest was opened through its periosteal bed. The lung was not adherent. The tumor could be palpated through the diaphragm. It extended into the lower esophagus but not far in the thoracic portion. The diaphragm was opened and retracted with stay sutures. The liver was palpated and no nodules were found within it. The carcinoma extended along the lesser curvature from the pylorus to the cardia and, although the greater curvature was free excepting near the fundus, it was obvious because of the extent along the lesser curvature that nothing short of a total gastrectomy would be of any value.

There were a number of large lymph nodes near the cardia and also on both sides of the pylorus which seemed to be involved. These were all removed. It was necessary to remove the spleen in order to get proper access to the region behind the stomach. The lower esophagus was freed. The left gastric vessels were cut and tied. The anastomotic branches around the hiatus of the diaphragm and the vasa brevia were likewise cut and tied. The entire stomach was then freed, but in order to get good access to the duodenum it was necessary to cut across the esophagus first. This was done, using Doctor Smithwick's clamp. A basting-stitch was then used to close over the esophageal cut end, and the clamp was removed. The dissection was then carried down to the duodenum and in cutting around the lymph nodes which lay there so that they could be removed, the duodenum was partially torn. The remainder was cut across and the open duodenal end was sutured with a first layer of Connell sutures and a second layer of Lembert sutures of silk. This was reinforced by suturing it into the head of the pancreas and applying a piece of omentum over that. A rent was then made in the transverse mesocolon and the proximal jejunal loop was brought up through it. There was just enough slack in the jejunum to allow an anastomosis without tension. The Smithwick clamp was used again on the jejunum and an aseptic anastomosis was performed, placing the esophagus on the efferent arm of the jejunal loop. The afferent arm was then folded over the anastomosis by the Roscoe Graham method. Before the anastomosis was started the jejunal loop had been fixed posteriorly to the crura of the diaphragm and some of the mediastinal pleura. A three-layer suture was used. An entero-enterostomy was then performed between the proximal and distal arms of the jejunal loop, using two layers of catgut. An attempt was made to thread the nasal catheter through the anastomosis without success. It was, therefore, left in the lower esophagus. A long piece of omentum was brought up and sutured around the anastomoses, completely covering over the loop which had been brought up. The diaphragm was then sutured loosely around the jejunal loop. The entero-enterostomy was just below the level of the diaphragm. The opening in the transverse mesocolon was not sutured.

Two Gm. of sulfanilamide was introduced in the abdomen and two in the chest. A catheter was brought out through the 9th interspace posteriorly, and the chest was closed.

Pathologic Examination.—Gross: The specimen showed a totally resected, previously opened stomach including the pylorus, measuring 30 cm. along the greater curvature and 12 cm. along the lesser. A small (0.5 cm.) piece of esophagus was also present.

Involving practically all of the lesser curvature and about a third of both anterior and posterior walls was a very hard, infiltrating tumor, measuring approximately 8 x 6 cm. The edges of the tumor were raised approximately 6 — 7 mm. and the main bulk of the tumor was ulcerated, reddish-yellow, and granular. The tumor extended very close to the pyloric cut edge. The entire muscularis and serosa in the region of the tumor was definitely infiltrated, producing irregular grayish-white subserosal plaques. *Pathologic Diagnosis:* Adenocarcinoma, with metastases to regional lymph nodes.

Roentgenologic examination of the chest three days after operation showed diffuse haziness throughout the left side, probably due to a small amount of fluid. There was no evidence of appreciable mediastinal shift.

The patient's postoperative course was uneventful and uncomplicated except for parotitis, which developed a week after operation.

Case 7.—M. G. H. No. 391651: I. P., male, age 57, was admitted to the Baker Memorial, January 29, 1943, because of what was thought to be a gastric ulcer. He had been perfectly well until ten months previously when he first noticed the onset of a tired feeling. His physician said that his blood was low and gave him vitamins and iron. This improved him considerably. In May, 1942, he had had a three-week episode of diarrhea, without blood or other symptoms. This had cleared spontaneously and except for occasional abdominal discomfort and gas he had been well until about eight weeks prior to admission, when he had had another attack of diarrhea without other symptoms. Four weeks before admission he had vomited about two cupfuls of blood, had fainted, and had been taken to a local hospital. He soon recovered, and a gastrointestinal series showed what was thought to be a gastric ulcer. He was, therefore, referred to the Massachusetts General Hospital for gastroscopy and treatment. He had had no nausea, vomiting, or cramps except as previously mentioned. His appetite had been good. He had lost about 12 pounds during his recent hospital stay but had regained some of that. He had no other symptoms.

Physical Examination.—The patient was a well-developed and well-nourished middle-aged white male. The heart and lungs were apparently normal. Abdominal examination was negative. Rectal examination was negative. There was no rectal shelf.

Laboratory studies showed a photohemoglobin of 10.7 Gm., serum protein 5.2 per cent N. P. N. 32 mg. per cent, and chloride 105.4 mg. per cent. The Hinton test was negative.

On January 30, 1943, gastroscopy was attempted but at the cardiac orifice the instrument met with complete obstruction, and no view of the stomach could be obtained. It was felt that the findings were consistent with neoplasm involving the upper part of the stomach close to the cardiac orifice and that the case was a suitable one for transthoracic gastrectomy.

Two days following gastroscopic examination the patient suddenly vomited about 700 cc. of bright red blood. His blood pressure fell to 90/50. He was transfused a number of times, with good response.

Operation.—February 10, 1943: A transthoracic gastrectomy with esophagojejunostomy, entero-enterostomy, and splenectomy were performed. A long oblique incision was made along the left side of the chest and the ninth rib was resected. There were a number of adhesions between the lung and diaphragm. These had to be separated. The lower end of the esophagus was identified and freed-up. A tape was passed around it. The diaphragm was opened. The growth was found to be operable and the phrenic nerve was, therefore, pinched. The growth extended from about 1.5 cm. below the cardiac orifice almost to the pylorus, and it was obvious that nothing short of a total gastrectomy would succeed. This was carried out. The spleen was removed in order to get better access. The duodenum was cut across on a Jones clamp and the duodenal end was inverted. The freed-up stomach, which was still attached to the esophagus, was then brought up and laid out on the chest.

An attempt was made to bring up the proximal jejunal loop. This was found to be impossible because of the widespread adhesions all over the abdomen between the loops of small intestine. It was impossible to get at these without enlarging the incision. The costal arch was cut and the incision extended downwards into the abdomen for a distance of about five inches. This gave good exposure, and, after considerable exploration and freeing of adhesions, it was possible to bring up a loop of jejunum just below the proximal loop. This loop, however, could not be brought up into the chest without dividing two of the large vessels at the base of its mesentery. After this was done the loop came up about three inches higher, and an anastomosis became possible.

In order to insure a proper emptying of the duodenum the jejunum just below the ligament of Treitz was anastomosed to the distal arm of the jejunal loop which was to be used for the esophagojejunostomy. A two-layer side-to-side anastomosis was made between these two loops of jejunum. The esophagojejunostomy was then carried out, using a transverse incision on one side of the jejunal loop. A three-layer silk anastomosis was made, the jejunal loop having been brought up through an opening in the transverse mesocolon. The opposite arm was wrapped around the anastomosis, somewhat after the method of the Roscoe Graham technic. The jejunum had previously been fixed by several interrupted silk sutures to the sides of the crura of the diaphragm and the tissues against the thoracic aorta. An entero-enterostomy was made between the two arms of this loop at this time, using a three-layer fine catgut suture. Thus, in this case there were actually two entero-anastomoses of the jejunum, one above and one below the transverse mesocolon.

The diaphragm was attached to the loop, and the remainder of the diaphragm opening was sutured with interrupted silk. The abdominal end of the wound was closed in layers, and after this the chest was closed in the routine fashion, bringing out a catheter through one of the lower interspaces. Two Gm. of sulfanilamide were placed in the abdomen and about two Gm. in the chest..

Pathologic Examination.—The specimen removed showed a stomach measuring 30 cm. along the greater curvature and 15 cm. along the lesser curvature. Along the lesser curvature, 7 cm. from the pyloric end, there was a fungating, ulcerating, gray-white, granular, infiltrating mass measuring 9 cm. in diameter and raised 2 cm. above the surface. The mass was infiltrating the muscularis and caused wrinkling of the overlying serosa. The mucosa throughout the entire specimen was markedly edematous. Fourteen soft, reddish-gray lymph nodes were found. There was a normal-appearing spleen weighing 143 Gm., and measuring 14 x 7 x 3 cm. The regional lymph nodes were negative, but the neighboring lymphatics were filled with tumor. *Pathologic Diagnosis:* Adenocarcinoma, Grade II, with chronic gastritis.

Following operation the patient did exceedingly well. On the seventh postoperative day he complained of some pain in his right calf, and on examination the right leg was found to be moderately tender to pressure in the right calf. The Homans' sign was negative. A ligation of the right common femoral vein was performed.

Check-up examination four months after operation showed the patient to be in excellent condition. He had returned to his work as a minister about two months previously. He swallowed well and had no discomforts relative to his intestinal tract.

The author wishes to express his gratitude to Dr. E. D. Churchill for the privilege of including Case I and to Dr. Robert R. Linton for Case III.

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CARCINOMA OF DUODENUM

ONE-STAGE RADICAL PANCREATICODUODENECTOMY, PRESERVING THE EXTERNAL PANCREATIC SECRETION

CASE REPORT

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THE SURGICAL TREATMENT OF CANCER involving the first and second portions of the duodenum, the ampullary region, and the head of the pancreas has recently been receiving an increased amount of attention. The reasons for this lie primarily in the discovery of methods whereby the bleeding tendency in jaundice can be controlled as well as in recent improvements in the pre- and postoperative care of debilitated patients. In view of the effectiveness of these surgical aids it has been possible during the past seven or eight years to change the status of radical pancreaticoduodenectomy from that of a rare surgical feat to one associated with an encouraging incidence of success.

Early in the renewed attack upon this problem efforts were made toward its accomplishment in two stages. The first of these, a cholecystenterostomy, was presumed important in order to control the bleeding tendency which is associated with the jaundice almost invariably present in patients suffering from cancer in and about the head of the pancreas. Early in the annals of the two-stage procedure it became evident that many technical difficulties were involved, particularly with reference to the number of adhesions encountered at the second stage. This, together with a fuller appreciation of the effectiveness of vitamin K in controlling the hemorrhagic tendency led Whipple, in 1940, to perform the first successful single-stage operation. Since then the trend has been definitely toward accomplishing this radical procedure at one operation.

The early history of this type of radical operation, 1900 to 1935, was associated with many unsuccessful efforts directed toward preserving the external pancreatic secretion, a factor presumed necessary to life because it was believed impossible to keep dogs alive following total pancreatectomy. This period was followed by one during the early part of which it was discovered that some patients could survive when deprived of their external pancreatic secretion. At the moment, the question of the absolute necessity of the external pancreatic function is far from finally settled. Apparently, if one is to judge from the reported cases, the state of health of the patients in whom no effort has been made to preserve this function is quite variable; some have shown a remarkable degree of fat digestion, while others have admittedly done poorly, steatorrhea and general debility presenting as a

prominent feature of their postoperative course. Perhaps the most significant single factor is that it is impossible to predict preoperatively which patients will tolerate deprivation of their external pancreatic function and which will not. These factors, together with the appreciation of the fact that pancreatico-enteric anastomoses can be successfully performed provided silk is employed as the suture material, have prompted the recent tendency to secure, if possible, drainage of the pancreas into the gastro-intestinal tract.

Because it has seemed advantageous to counter further the impression, all too generally held, that pancreaticoduodenal cancer is therapeutically hopeless, the following case is added to those already reported. It is that of a patient with carcinoma, primary in the duodenum, in whom a radical pancreaticoduodenectomy was performed in one stage. He survived, relatively free of symptoms, for 14 months, at the end of which period reexploration of the abdomen because of jaundice revealed massive recurrence of the tumor.

Case Report.—N.Y.H. No. 311583: J. B., white, male, age 57, was first admitted to the New York Hospital in November, 1941, complaining of generalized cutaneous pruritis and of jaundice, both of one month's duration. His family history was irrelevant save that his father died of carcinoma of the stomach. Detailed inquiry into his past history failed to reveal any significant facts prior to the onset of his present illness. This the patient dated to approximately four weeks before admission, at which time he suffered from diarrhea for one week. During this his stools became lighter in color, his urine darker, and his skin yellow. Associated with these phenomena, his appetite became poor, he developed generalized pruritis, and lost 20 pounds in weight. On admission, his vital signs were within normal limits and physical examination revealed a well-developed, chronically ill man, who was intensely jaundiced. There were no significant abnormalities noted in the course of his general examination. Interest centered in examination of the abdomen where, in the right upper quadrant, an enlarged liver and gallbladder were palpable. There was no tenderness, nor could any tumor masses be felt.

Laboratory Data (preoperatively):

Blood—Hb., 10 Gm.; RBC, 3.8 M; WBC, 9050. Differential normal.
Urine—Negative save for the presence of a marked amount of bile.
Icteric index—110 mg./100 cc.
Stool—Guiaic, 2+
Prothrombin time—61%, rising to 100% after administration of vitamin K.
Duodenal drainage—Bile absent, indicating complete common duct obstruction.
Secretin test—Marked increase in volume after administration of secretin:

Volume	—501 cc.
Bicarbonate	—96 milliequivalents
Total output	—382 (N/10 $NaHCO_3$
Diastase	—673 units per 60′
Trypsin	—115 units per 60′
Lipase	—31,886 units per 60′

Interpretation: These figures are high normal, and fail to indicate any obstruction of the pancreatic ducts.

Blood sugar —78
Blood urea N.—11

Roentgenologic Examination.—(11/27/41): The stomach, esophagus and duodenal bulb are normal. The second and third portions of the duodenum are very irregular in outline. A mass is noted in the third portion. Chest normal. *Diagnosis:* Infiltrative carcinoma of the head of the pancreas. Carcinoma of the duodenum.

Preoperative Course: In view of the jaundice; failure to obtain bile on duodenal drainage; the defective appearance of duodenum when visualized with barium as a contrast media; and normal pancreatic function, a diagnosis of carcinoma was made, primary in either the common duct, the duodenum, or the pancreas, and associated with obstruction of the common duct but not of the pancreatic ducts.

Operation.—November 28, 1941: Under open drop ether, the peritoneal cavity was entered through a long right upper rectus incision. The liver was found enlarged but without evidence of metastatic involvement. The gallbladder and common duct were hugely dilated. There was a hard tumor mass involving the second portion of the duodenum, the region of the ampulla of Vater, and the head of the pancreas. This was

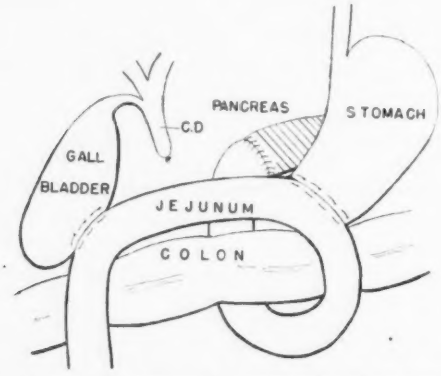

FIG. 1.—Diagrammatic representation of the reconstruction of the continuity of the gastro-intestinal, biliary and pancreatic tracts.

freely movable, and resection was undertaken as follows: (1) The right lateral peritoneum was divided as was the gastrocolic ligament, thereby mobilizing the entire duodenum; (2) the common duct was divided; (3) the jejunum was divided just distal to Treitz' ligament; (4) the lower end of the stomach was divided; (5) the pancreas was divided at approximately the junction of its distal and middle third; (6) the tumor and associated structures were then carefully freed from the vena cava and superior mesenteric vessels and removed; (7) reestablishment of the enteric canal and associated organs was accomplished by the following anastomoses: (a) Gastrojejunostomy, end-to-side; (b) pancreaticojejunostomy, end-to-end; (c) cholecystojejunostomy, side-to-side (Fig. 1). The wound was closed with through-and-through silver wire and catgut in layers, draining the right gutter through a stab wound in the flank. One drain was placed near the site of pancreaticojejunostomy. Time—five hours.

Pathologic Examination.—Gross: The specimen consists of a segment of duodenum 14.5 cm. in length and 6 cm. in circumference. The last 5 cm. of the duodenum is occupied by a crateriform tumor which surrounds the intestine completely. The ampulla of Vater presents as a lobular mass 2 cm. in width and 9 cm. in thickness; the orifice admits a 3 mm. probe. The common duct above the ampulla is dilated to a circumference of 3.5 cm. The walls are leathery and are invaded by tumor only in the distal portion, where it traverses tumor. The accessory pancreatic duct is patent to the same probe and is not involved in tumor, emerging through duodenal mucosa about 5.5 cm. above the ampulla of Vater. The bile-stained head of the pancreas is stony-hard and apparently

shares with the duodenum in its carcinomatous involvement. The duct of Wirsung cannot be demonstrated beyond a small tract which opens near the papilla of Vater in the common duct and runs about 3 cm. along its wall, beyond which point a probe will not pass. With the specimen is 11 cm. of uninvaded, natural-looking jejunum. As the body of the pancreas is sectioned the main pancreatic duct is identified. By means of a probe this duct can be traced through the substance of the pancreas to emerge at the obstructed ampulla of Vater.

Microscopic examination of the duodenum reveals that there is very poorly-differentiated epithelium growing in a wild and disorderly fashion throughout the thickness of the wall. This epithelium consists of cells which vary considerably in size, shape and staining quality, but are, for the most part, somewhat polygonal. They are arranged in strands and cords and in some places have a tendency to form rudimentary alveoli, which do not contain lumina. A notable feature of these epithelial cells is that many of them resemble mucous cells. Many of them assume the form of "signet rings." Although it is unusual, there is no doubt that this tumor originates in the duodenum rather than in the papillary epithelium, as do the common ampullary tumors.

Postoperative Course.—The immediate postoperative course was marred by the development of atelectasis of the right lower lobe, followed by pneumonia. This, however, cleared within a few days upon the administration of sulfadiazine. The abdominal wounds healed without infection, and the drains were removed on the seventh postoperative day, their stab wound closing within the next few days. He was discharged from the hospital upon the 30th day after operation.

During his postoperative period two laboratory studies were of interest. (1) His preoperative fasting blood sugar was 78 mg./100 cc. Immediately following operation this ranged from 120 to 153 mg./100 cc., though at no time was there a glycosuria. On discharge the fasting level was 100 mg./100 cc. (2) The secretin test was repeated, and the values were as follows:

Volume	—1.75 cc./kg./57′
Bicarbonate	—16 milliequivalents
Diastase	—0.76 units/kg./57′
Trypsin	—0.26 units/kg./57′
Lipase	—104 units/kg./57′

Interpretation: This demonstrates the presence of external pancreatic secretion in the gastro-intestinal tract, there being approximately one-sixth of normal function present. In view of the fact that this man manifested no abnormality in fat digestion, it must be assumed either that the collection of the material was far less efficient than in the normal or that one-sixth of the normal amount is adequate for normal digestion of ingested fat. Which of these approaches is correct is of course impossible of determination.

During the first 14 months following operation this man was entirely well save for two attacks of chills, fever, and transient jaundice—interpreted as attacks of ascending cholangitic infection, a phenomenon not infrequently observed following cholecystenterostomy. At the end of this period he again became jaundiced and was readmitted to the hospital.

Physical examination at this time revealed an enlarged liver, upon the surface of which could be palpated several hard nodules. Although the outlook, of course, was not good it was felt that he deserved reexploration in the hope that revision of the cholecystenterostomy could be undertaken and the patient relieved of his jaundice. At operation, under local anesthesia, March 8, 1943, the entire peritoneal cavity was found studded with small metastatic nodules. The anastomosis between the gallbladder and

the jejunum was visualized, and it, too, was the site of numerous metastatic nodules partially occluding the stoma. Microscopic section of the small nodule removed at operation showed recurrent carcinoma.

DISCUSSION.—DR. ALLEN O. WHIPPLE (New York): My chief objection to this modification is that the common duct is tied off, and the gallbladder is anastomosed to the jejunum distal to the gastro-enterostomy. This means that the chances are more than even that the ligature will cut through the common duct, with a resultant biliary fistula—usually a fatal complication.

A NEW CONCEPT REGARDING THE ORIGIN OF SO-CALLED PRIMARY CARCINOMA OF THE HYPERPLASTIC THYROID*

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THE STRIKINGLY RARE OCCURRENCE of carcinoma in diffuse toxic goiter as compared with its relatively frequent occurrence in preexisting adenomatous goiter excites speculation as to the reason for this wide difference in the incidence of malignancy in these two types of goiter. One may readily believe there is a peculiar reason for the rare discovery of malignancy in exophthalmic or diffuse hyperplastic goiter, particularly in view of the abundant opportunities for pathologic examinations of tissues obtained by resection operations on large numbers of hyperplastic thyroid glands. It appears, at once, that adenomatous goiter is the outstanding culprit in the origin of carcinoma by virtue of its predisposition to malignant degeneration and that the relatively rare coexistence of true adenoma and hyperplastic goiter may, therefore, well be the principal reason for the infrequent occurrence of carcinoma in exophthalmic or hyperplastic goiter. A secondary consideration is the question whether carcinoma in reality ever occurs as a primary lesion in diffuse parenchymatous hyperplasia of the thyroid gland.

In previous reports on malignancy of the thyroid it is repeatedly stated, that carcinoma has not been encountered in the hyperplastic gland of exophthalmic goiter. Thus, Wilson[1] found no instance of malignancy in the hyperplastic gland in a series of 290 patients with malignant tumors of the thyroid observed at the Mayo Clinic. Observations on 55 cases of malignancy of the thyroid by Simpson[2] accorded with Wilson's findings. However, in more recent writings we find the occasional report of a malignant tumor arising in the hyperplastic gland of exophthalmic goiter, as in the one instance of malignant neoplasm occurring in a series of 90 epithelial malignant neoplasms reported by Coller.[3] C. W. Mayo[4] stated, on the basis of a study of 737 cases of malignancy of the thyroid, occurring at the Mayo Clinic, that more than three per cent of the cases of adenomatous goiter, in which operation was performed, were malignant; and that approximately 50 per cent of malignant growths of the thyroid were within adenomata. In a subsequent report of 774 instances of malignancy of the thyroid observed in this same Clinic, Pemberton[5] stated, in agreement with most writers on the subject, that the presence of a preexisting benign adenoma is the most important known etiologic factor in the development of thyroid carcinoma. The association of malignancy and exophthalmic goiter was encountered in ten patients in his series; in four the malignant lesion was confined to an adenoma, and in six

* An abstract of this report was presented at the meeting of the American Association for the Study of Goiter, Rochester, Minn., April 15, 1940.

it developed within the gland itself. Thus, it appeared that in only six instances in the series of 774 malignancies, the malignant lesion occurred in the hyperplastic gland itself. According to previous writers the incidence of malignant tumor arising in preexisting benign adenomata varies between 80 and 95 per cent. In a personal communication, Pemberton stated that the percentage of malignant tumor that arose from preexisting benign adenomata, in his experience, was 87 per cent, calculated on a combined pathologic and clinical basis, but that this figure was subject to errors of interpretation. Welti and Huguenin[6] stated that in 88 patients with malignancy of the thyroid, 38 had noticed a preexisting goiter for more than eight years, and that in the 50 malignancies occurring without preexisting goiter the evolution of the tumors may have taken several years and may have been carcinoma from the beginning. They stated, further, that carcinoma rarely, if ever, develops in the hyperplastic thyroid of exophthalmic goiter.

Malignancy of the thyroid was found in 52 patients operated upon at the Long Island College Hospital during the ten-year period from 1930 to 1939, inclusive. There were seven instances in which the malignancy occurred in the hyperplastic exophthalmic gland. In four of these malignancy appeared to be primary, at any rate, there was no discernible preexisting adenoma, while in the remaining three the carcinoma definitely had its origin in a coexisting adenoma. In 37 instances the carcinoma arose in adenomatous goiters which were recognized clinically and by pathologic examination.

The suspicion that carcinoma occurring in exophthalmic goiter may have had its origin in an incidental, minute fetal adenoma occurred to the writer ten years ago following the discovery of a small, white, stellate, fibrous nodule, five millimeters in diameter, which occurred in the resected gland from a patient with exophthalmic goiter, and which, upon microscopic examination, proved to be adenocarcinoma. It was, furthermore, noted that the epithelial cells in several areas within the nodule appeared to be of the embryonic or so-called fetal type. It was thought that these cells may well have had their origin in a minute fetal adenoma the identity and recognition of which had been effaced by the multiplication and diffusion of the malignant cells. At any rate, a true encapsulated adenoma was not clearly discernible. During the past ten or twelve years we have been on the lookout for similar lesions in the hyperplastic thyroid gland with the hope that we might be successful in demonstrating that the incipient carcinomata in these instances as a matter of fact, had their origin in true minute fetal adenomata. A minute carcinomatous lesion, definite or strongly suspected, was found in each of nine instances of hyperplastic (exophthalmic) goiter. In three of these we were fortunate enough to discover upon microscopic examination a minute, well-defined and encapsulated adenoma enclosed within the small fibrous nodule, and showing what appeared to be unquestioned carcinomatous degeneration. Practically all the histologic criteria of malignancy, including even the invasion of blood or lymph vessels, were revealed in the sections. The findings in the fourth nodule strongly supported the diagnosis of malig-

nancy. In three further instances the nodules showed scirrhous carcinoma in which, however, no evidences of a preexisting adenoma were found. In another nodule papillary adenocarcinoma was strongly suspected. In the ninth case the origin of an adenocarcinoma in a preexisting adenoma was suspected because of the appearance of the cells enclosed within the lesion. These were definitely of the embryonic so-called "fetal" type. Finally, passing mention may be made of unquestioned adenocarcinoma arising in a minute adenoma occurring in an otherwise normal gland. Naturally, a considerable number of lesions proved to be of simple benign nature, and resembled those to which Graham[8] has drawn attention.

The material forming the basis for the present study consisted of blocks of tissue cut from the resected specimens of hyperplastic (exophthalmic) goiter in such a manner as to incorporate in their centers the minute whitish nodules suspected of malignancy and previously described in the introduction. Tissues were fixed in formalin and Zenker's solutions and sections prepared, in serial manner, at frequent levels in order to be representative of the detailed histopathology in all parts of the lesion. Sections were stained with hematoxylin and eosin for general histology and, after the Pappenheimer methyl-green pyronine method, described by Mallory,[9] for the demonstration of plasma cells.

It is our purpose to report in detail the gross and microscopic findings in two cases of exophthalmic goiter in each of which a minute carcinomatous lesion, measuring 0.5 cm. in greatest diameter, was found to enclose a circumscribed and encapsulated adenoma, which had undergone malignant degeneration and which was shown to be the point of origin of the malignant lesion. These findings together with those observed in seven further, proved or suspected, instances of minute incipient carcinomata occurring in the hyperplastic thyroid will be considered in the discussion and summary. In one of these seven cases, the origin in adenoma was demonstrated, and in three such origin was strongly suspected. It is hoped that these findings will aid in establishing the fact that primary carcinoma rarely, if ever, occurs in the hyperplastic thyroid gland and that when carcinoma does occur its origin in a minute adenoma has been obscured by the overgrowth of the lesion. The findings are intended, further, to establish the classification of primary or secondary carcinoma in hyperplastic goiter.

CASE REPORTS

Case 1.—D. J., female, age 24, was first seen January 5, 1937, at which time she complained of symptoms of hyperthyroidism of four months' duration. Upon examination she showed exophthalmos and a diffuse moderate fullness of the thyroid gland which exhibited thrills and bruits at the poles. Cardiac action was accentuated and the pulse was 146. The basal metabolic rate was +74 per cent, and after preparatory treatment of the patient with Lugol's solution it had declined to +24.6 per cent above the average normal. The preoperative diagnosis was exophthalmic goiter with marked hyperthyroidism.

Operation.—Double lobectomy was performed on January 18, 1937.

Pathologic Examination.—Gross: The resected thyroid gland had the usual colloid appearance of hyperplastic goiter after the administration of iodine. Both the gross and microscopic appearances confirmed the diagnosis of hyperplastic goiter. The resected portion of the right lobe was cut longitudinally, whereupon a small whitish, indurated nodule, measuring 0.5 cm. in greatest diameter, was exposed. In the center of the lesion there was a minute nodule, which measured 2 mm. in diameter, and which was surrounded by a narrow zone of fibrous reaction. Tentatively, this whitish lesion was considered to be carcinomatous. A block of gland comprising the lesion and a generous area of surrounding thyroid was cut from the specimen and prepared for sectioning.

Sections were cut in serial fashion at frequent intervals beginning with the most superficial portion of the lesion. The findings in four sections at different levels (Fig. 1, A, B, C, D) are reported.

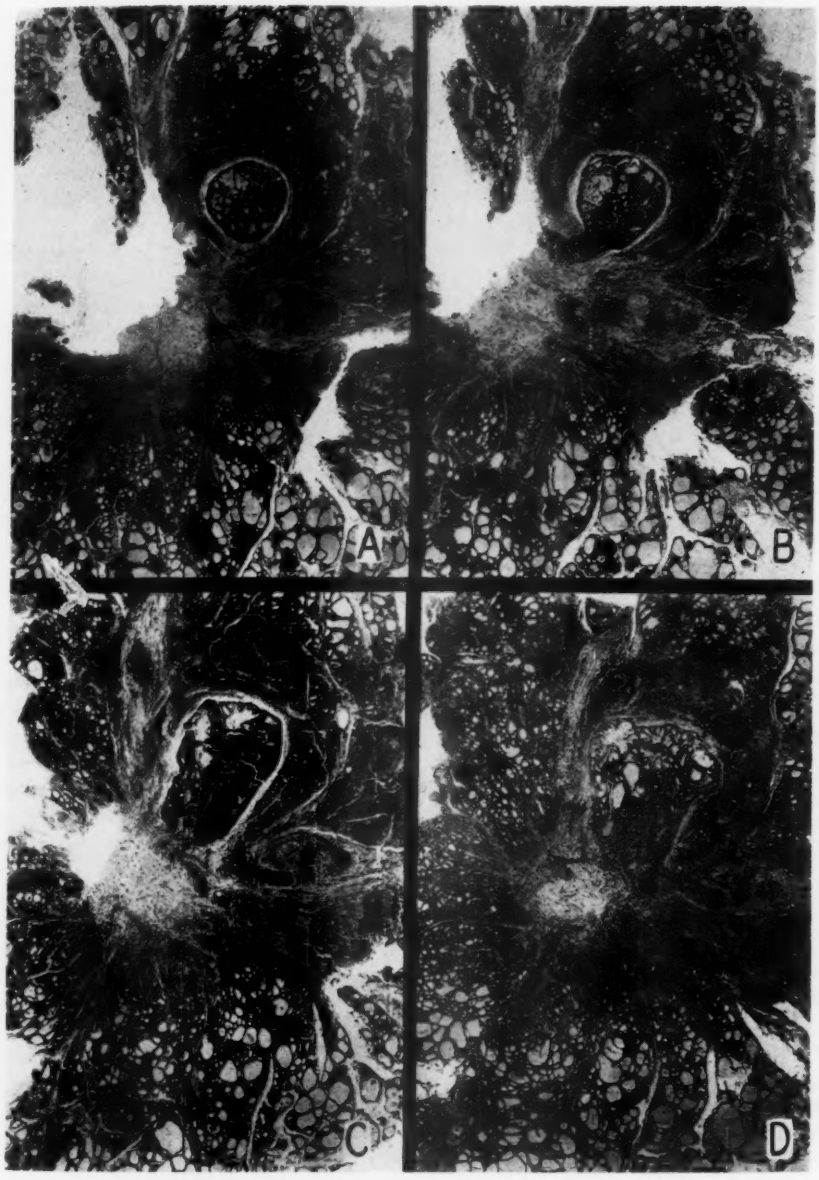
Microscopic Description.—Low Power: Section A (Fig. 1) represented a section through the superficial portion of the lesion. In the center of the section was a discrete, rounded, well-defined and encapsulated nodule, which measured approximately 1 mm. in diameter. This nodule was composed of densely blue-staining, tortuous cords of cells with dark staining nuclei and without definite acinous structure. No colloid was visible. In one zone, comprising approximately one-third of the nodule, there were irregular clear areas composed of hyalinized connective tissue in which remnants of acinar epithelium were seen. In another area numerous small masses of blue-staining calcium granules were noted. Immediately surrounding the nodule there was a wide zone of compressed lobular gland composed of minute acini containing droplets of colloid. Further peripherally there was a large area of dense hyaline pink-staining fibrous tissue, in the meshes of which there were cellular accumulations. Radiating strands of connective tissue arising from this hyalinized area were seen penetrating the surrounding normal appearing gland. There was a gradual transition from the irregular, diffusely cellular areas to the surrounding normal appearing gland.

High Power: The interior of the central nodule was composed largely of wavy, papillary columns of compact lining cells containing large, deeply-staining nuclei. There was no tendency to the formation of normal acini. The low columnar cells lining the cords were often arranged in reduplicated layers. The nuclei of these cells were mostly large, rounded, oval and irregularly shaped, with the long axes perpendicular to the basement membrane. They were hyperchromatic, deeply-staining and many of the smaller ones were densely pyknotic. The stroma between these cords was scant. Between the cords infiltrated cells of various types including lymphocytes, polymorphonuclear, epithelioid and a few plasma cells were seen. In addition to the rather definite papillary cords there were also large groups of well-defined cells with huge hyperchromatic nuclei.

Adjoining the area of papillary cord formation was another area of numerous closely aggregated cells with large, rather pale nuclei and with a scant vacuolated protoplasm. These cells gave the impression that they were undergoing degeneration. There was no definite structural arrangement. Scattered through this area, furthermore, were numerous masses of calcium granules. A third area within the nodule was composed largely of hyalinized connective tissue containing few nuclei and remnants of more or less well-defined acinar lining cells, many of which were atrophied and degenerating. Here, also, several masses of calcium granules were seen. No colloid was apparent anywhere in the nodule.

The thin capsule of the nodule was composed of broad concentric bands of hyalinized fibrous tissue in which there were relatively few nuclei of various sizes and shapes. Immediately outside of and adjoining the capsule there was a relatively large zone of anastomosing bands of connective tissue, in the spaces of which there were small, compressed thyroid acini which appeared atrophic and practically without colloid. In addition, in these spaces there were masses of cells of every description. Some cells had huge, pale-staining, rounded nuclei, while others contained nuclei irregular in shape,

A B



C D

FIG. 1.—Case 1: Photomicrographs (×12) of four representative sections at different levels in a small scirrhus carcinoma occurring in exophthalmic goiter. Note in the center of the lesion a minute adenoma, the site of the primary papillary adenocarcinoma which had perforated the capsule of the adenoma.

A. Superficial section of the encapsulated adenoma and the surrounding scirrhus carcinoma.

B. Section at a deeper level showing perforation of the capsule by the papillary neoplasm which is extending beyond the confines of the adenoma.

C. The section at this level shows a large defect in the capsule and the hyalinized fibrosis opposing the extension of the malignant growth.

D. Section showing the wide area of scirrhus carcinoma and in its center the papillary primary neoplasm still confined to the adenoma.

densely stained and often pyknotic and shriveled in appearance. These cellular masses showed no definite glandular structure and loosely aggregated cells were often seen filling what appeared to be lymphatic and vascular spaces. Numerous lymphocytes in small aggegations, large numbers of plasma cells and occasionally polymorphonuclear cells were seen. Finally, peripheral to this area of fibrous reaction there was a wide zone of dense cellular infiltration without definite architecture and composed of large cells with hyperchromatic, oval, irregular nuclei, some of which showed chromatin figures. Surrounding groups of these large irregular cells, lymphocytes and plasma cells in large numbers were recognized. By gradual transition this infiltrated cellular zone finally assumed the appearance of the contiguous normal exophthalmic gland.

A second section (Fig. 1, B), which illustrated the appearances at a deeper level in the lesion, showed the following histologic findings:

Low Power: The central nodule presented appearances in many respects similar to those just described for Section A. The striking finding, however, was the opening in the capsule through which a dense stalk of tissue, composed of cellular epithelial cords, was seen extruding itself and invading the surrounding tissue which showed an extreme hyaline fibrosis. In general the findings in the zone of reaction in the gland surrounding the nodule were much the same as those described for Section A.

High Power: A large opening in the capsule of the nodule was seen through which protruded a thick column composed of cellular epithelial cords. Between the cords could be seen a small amount of stroma containing numerous lymphoid, plasma and epithelioid cells. The cords were lined by low columnar cells, the nuclei of which varied greatly in size and shape. Some were huge, some small and oval in shape, while others were distorted and pyknotic. Colloid-containing acini were not apparent. Closely adjacent to the lesion these cords became separated into ill-defined islands of epithelial cells by the penetration of strands of hyalinized fibrous tissue in the spaces of which masses of large, hyperchromatic nuclei of cells without any definite arrangement were seen. Surrounding the nodule there was a wide zone of small ill-defined thyroid acini practically devoid of colloid. Numerous lymphocytes and plasma cells were seen between the acini. Apposing the point of perforation of the nodule there was a large area of hyalinized fibrous tissue in the spaces of which were seen irregular masses of cells consisting of large epithelial cells with huge hyperchromatic nuclei, lymphocytes and numerous plasma cells. From this hyalinized fibrous zone strands of connective tissue radiated outwards into the more normal appearing thyroid parenchyma.

A third section, representative of appearances at a still deeper level in the nodule (Fig. 1, C), revealed the following findings:

Low Power: The nodule at this deeper level was still well-defined and encapsulated but larger and more oval than in the previous sections. In general, it had the appearance described for the previous section (Fig. 1, B). It was composed of wavy, cellular cords, many of which were arranged in approximately parallel rows. There was a zone of dense hyaline connective tissue reaction around the cellular tissue extruded through the rent in the capsule. From this dense zone of fibrosis, radiating strands of connective tissue penetrated the surrounding more normal appearing gland. Large cellular aggregations without definite structure were seen between these radiating strands of connective tissue.

High Power: The capsule of the nodule was well-defined and made up of concentric layers of hyalin connective tissue containing moderate numbers of flattened nuclei. The nodule was composed of several large, irregular acini, many small acini and numerous parallel cords of epithelial cells. The lumina of the largest acini contained a granular pale-staining colloid in which could be seen numbers of fibroblasts, some free epithelial cells and a few lymphocytes. In some areas the colloid seemed to have undergone organization, as definite pink-staining fibrous tissue was recognized. The acini and cords throughout were lined by low columnar cells with oval nuclei which were closely

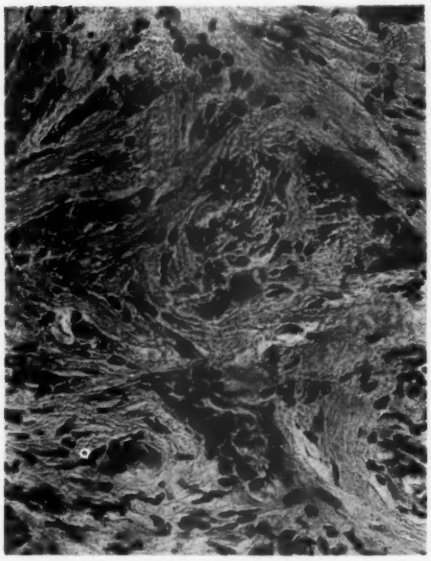


FIG. 2.—Case 1: Photomicrograph (×300) showing aggregations of epithelial cells in the spaces of the hyalinized fibrous tissue at the point of perforation of the adenoma. The cells and their nuclei varied greatly in size, shape and general character, and definite mitotic figures were noted (See Fig. 3).

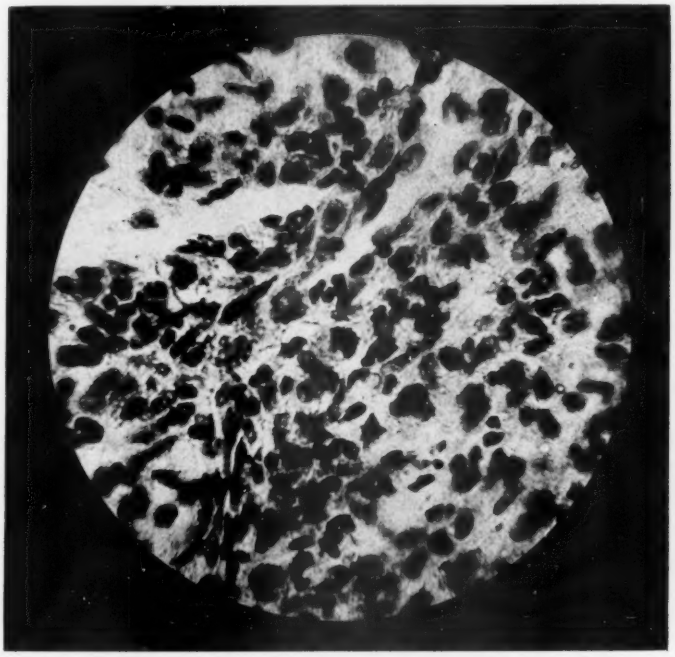


FIG. 3.—Case 1: Photomicrograph (×450) showing the variation in size, shape and chromatin content of the malignant cells enclosed in spaces of the fibrous stroma illustrated in Figure 2. Note the mitotic figure in the center.

assembled, deeply-staining and rich in chromatin. In some areas the lining cells were reduplicated. A minimum amount of stroma was seen. Here and there small masses of calcium were noted. The nodule was surrounded, except at the point of perforation, by a zone of densely packed small acini, between which one could recognize groups of lymphoid cells, plasma cells and occasional polymorphonuclear leukocytes. In some areas acinar formation was ill-defined. The findings in the zone of reaction adjacent to the point of perforation of the nodule were not unlike those described for the previous two sections (Sections A and B), except that the cellular infiltration was even more irregular and diffuse and was demarcated into islands by strands of hyalin connected tissue (Fig. 2). The epithelial cells aggregated in these islands were of every conceivable size, shape and general character. Many huge pale-staining nuclei containing granular chromatin were seen, while the nuclei in other instances were shrunken, shriveled and pyknotic. Definite mitotic figures were present (Fig. 3). Intermingled with

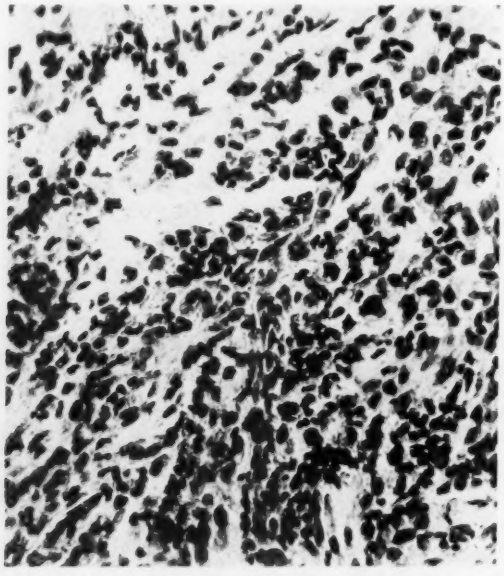


FIG. 4.—Case 1: Photomicrograph (× 300) illustrating the appearance of the cellular conglomerates in the meshes of the fibrous tissue reaction about the adenoma. Large numbers of epithelial cells with hyperchromatic nuclei and of varying size and shape together with lymphocytes, polymorphonuclear and plasma cells were noted.

these epithelial cells, groups of lymphocytes, plasma cells and occasionally polymorphonuclear cells were seen. The strands of hyalin connective tissue radiated outwards and penetrated the adjacent relatively normal appearing gland. Between these strands of connective tissue there were dense cellular accumulations consisting of large epithelial cells with large irregular nuclei, lymphocytes and plasma cells. Here, again, occasional mitotic figures were seen.

A fourth section (Fig. 1, D) showed, deeper in the lesion, appearances as follows:

Low Power: At this deeper level the microscopic section indicated that the nodule was larger and less well encapsulated than in the more superficial sections previously described. About one-half of the circumference was in immediate contact with a large hyalinized zone of fibrous tissue while in other respects the findings were similar to those in the previous sections already described.

High Power: A more decided branching of the cellular cords was noted. The

stroma between the cords had a myxomatous appearance and contained elongated spindle-shaped fibrillar cells and numerous small congested capillaries. In other areas the stroma between the cords of cells contained an abundance of plasma cells and lymphocytes. Polymorphonuclear cells were infrequent. There was an intense hyalin connective tissue reaction around the nodule. The meshes of this tissue contained groups of conglomerate epithelial cells without definite arrangement and with hyperchromatic nuclei of varying size and shape (Fig. 4). Between the larger cells there was an infiltration of plasma cells, lymphocytes and polymorphonuclear cells. Some of these spaces, giving the impression of vascular or lymphatic spaces, were crowded with large epithelial cells. Small masses of chromatin granules were recognized suggesting karyorrhexis. A wide zone of cellular infiltration extended from the nodule into the surrounding more normal appearing gland.

Pathologic Diagnosis: Small scirrhus carcinoma occurring in exophthalmic goiter and secondary to papillary carcinoma originating in a minute adenoma, the capsule of which had been perforated by the malignant neoplasm.

Comment.—The carcinomatous lesion in this case might readily be considered primary in hyperplastic goiter had it not been for the discovery of a minute encapsulated adenoma in the center of the growth. The malignant degeneration of the adenoma had involved and perforated the capsule and begun to invade the surrounding thyroid parenchyma. In the further overgrowth of the lesion the true origin in adenoma would have been obscured and the diagnosis of "primary carcinoma not arising in adenoma" would have been a natural one.

FIG. 5.—Case 2: Photograph of the resected left thyroid lobe in a case of exophthalmic goiter. Note the white nodule, 0.5 cm. in diameter, which proved to be a typical scirrhus carcinoma. In the center of this lesion a minute adenoma, 1 mm. in diameter, was found to be the site of a papillary adenocarcinoma, which thus proved to be the primary lesion.

Case 2.—G. M., male, age 40, was first seen March 8, 1938, when he complained of symptoms of hyperthyroidism of six weeks' duration. His outstanding complaint was fatigue. A unilateral exophthalmos, tremor, and evidences of marked loss of weight were noted. The thyroid gland was moderately enlarged and showed mildly positive vascular signs at the poles. The pulse was 96, and the basal metabolic rate, after the period of preparation with iodine, was 20 per cent above the average normal. The preoperative diagnosis was exophthalmic goiter with moderate hyperthyroidism.

Operation.—Double lobectomy was performed March 23, 1938.

Pathologic Examination.—Gross: The resected thyroid gland gave the appearance of increased colloid content characteristic of the hyperplastic thyroid gland after the administration of iodine. The preoperative diagnosis of hyperplastic goiter was verified after study of the microscopic preparations. Section through the left lobe near its inferior pole disclosed a small, firm, whitish lesion, about 0.5 cm. in diameter (Fig. 5). The surface of this lesion presented a stippled appearance, and minute strands of fibrous tissue were seen radiating in stellate fashion outward from the lesion. The gross ap-

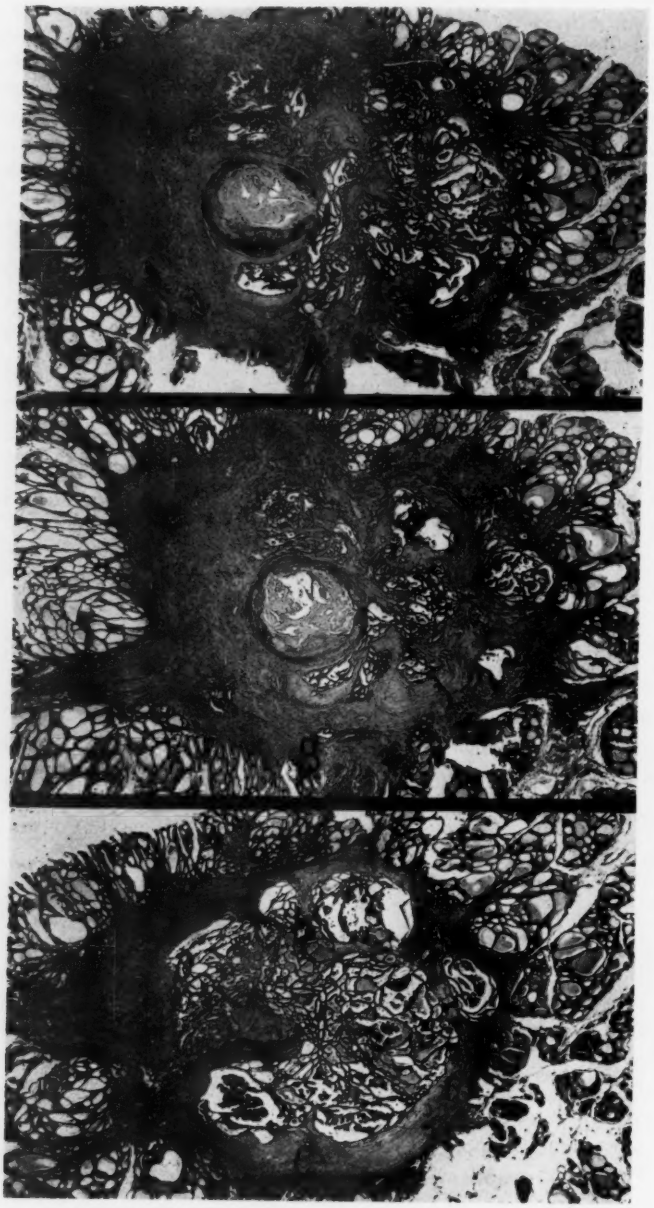


FIG. 6.—Case 2: Photomicrographs (×12) of sections of scirrhus carcinoma occurring in exophthalmic goiter and secondary to a primary malignancy of a minute adenoma.

A. Section through the center of the adenoma and the surrounding scirrhus carcinoma showing, on the right, perforation of the capsule and the adjoining area of papillary carcinoma while to the left an area of scirrhus carcinoma borders on the nodule. Note the central necrosis in the adenoma and the subcapsular darker zone of calcium deposit.

B. Section at a deeper level.

C. Section through the very periphery of the nodule, the capsule of which is still recognizable as a central area of fibrous tissue. Note the large area of papillary carcinoma which had overgrown the primary nodule.

pearance suggested the possibility of malignancy. A block of gland including the whitish nodule was cut from the specimen. Microscopic sections, cut in serial fashion, were then prepared in the usual manner. Three representative sections from different depths in the lesion and beginning at approximately its middle were chosen for detailed report of the microscopic findings.

Microscopic Description.—Low Power: Section A (Fig. 6) through the center of the lesion, showed a rounded, encapsulated nodule, slightly over 1 mm. in diameter, which was embedded in a zone of dense hyalinized fibrous tissue. The interior of the nodule was composed largely of a lightly pink-staining, degenerated, semihomogeneous tissue in which the outlines of large and small acini were visible as empty-appearing spaces, the lining walls of which showed occasional small atrophic nuclei. These spaces

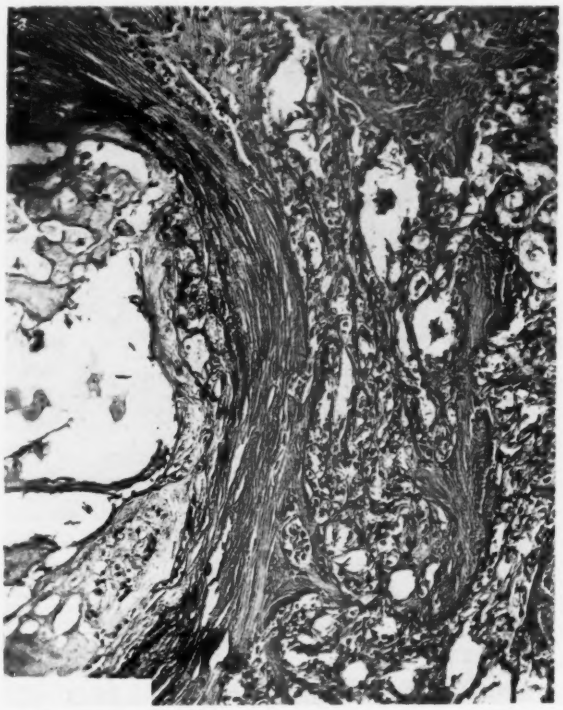


FIG. 7.—Case 2: Photomicrograph (×85) of a section including the margin of the adenoma (Fig. 6, A) with its capsule and the adjacent extracapsular area of papillary carcinoma. Note the papillary cords of low columnar cells in poorly defined acinous formation and, on the left, the necrosis within the adenoma.

doubtless represented the lumina of former acini. Surrounding this area of degeneration and immediately under the capsule of the nodule there was another well-defined zone of pink-staining ground substance in which were seen deeply blue-staining granular deposits of calcium. The nodule was enclosed in a well-defined capsule of hyalinized fibrous tissue and at one pole the capsule was extremely thin and gave the appearance of having been perforated. Adjacent to this point of apparent perforation there was a wide area of large and small anastomosing bands or septa of hyalinized connective tissue enclosing acini which were irregular in size and which showed numerous papillary infoldings of the lining cells. At the opposite pole the adenoma was partially surrounded by a dense zone of homogeneous hyalinized fibrous tissue, in the small lacunae of which accumulations of cells without particular arrangement were seen.

High Power: In the high power magnification, the adenoma showed a relatively large central area of degenerated, lightly pink-stained ground substance in which irregular empty spaces of varying size were seen. The lining walls of these spaces showed an occasional atrophic nucleus, and gave the definite impression of being the remnants of former thyroid acini. Normally staining thyroid tissue was not found within the nodule. Immediately under the capsule of the adenoma there was a fairly wide zone composed of fine hyalinized fibrils, in the meshes of which an abundance of blue-stained granules of calcium were seen. The thick capsule was composed of concentric layers of dense hyalin connective tissue containing only occasional atrophic appearing nuclei. Adjacent to the nodule at the point of thinning and evident perforation of the capsule, there was a large irregular area of anastomosing bands of hyalin fibrous

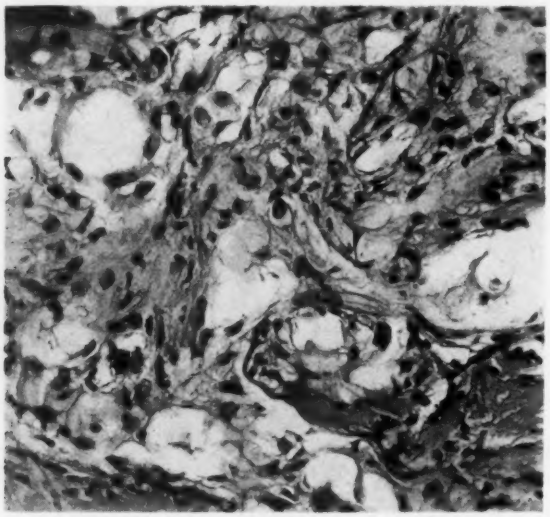


FIG. 8.—Case 2: Photomicrograph (× 300) of the papillary carcinomatous area adjacent to the adenoma (Fig. 6, A), and illustrated in Figure 7. Note the variation in shape and size of the hyperchromatic nuclei and the complete lack of glandular architecture. The protoplasm of the cells is scant in amount and irregular masses of chromatin are seen in the nuclei.

tissue enclosing irregular small and large acini many of which showed papillary projections of the lining walls (Fig. 7). The lining cells were low columnar or cuboidal, their protoplasm was granular and contained nuclei some of which were large and palely-stained while others were small, shrunken, irregular in shape and deeply stained. Occasional reduplication was seen. Some of the acini contained a thin granular colloid which was crenated, or vacuolated, while others contained a minimal amount of granular colloid and a few desquamated cells. In some of the smaller connective tissue spaces groups of large cells with scant protoplasm and irregularly shaped hyperchromatic nuclei were noted. These cells lacked definite arrangement. In one rather large area there was a great diversity in shape and size of the hyperchromatic nuclei and there was complete lack of normal glandular architecture (Fig. 8). The protoplasm of the cells was scant and occasional nuclei contained irregular chromatin masses but definite mitotic figures were infrequent. In one area, between the lesion and the adjoining normal gland, there was a focal area of infiltration of lymphocytes, plasma cells and a few polymorphonuclear cells. From the margin of the lesion, connective tissue strands were seen radiating into the adjoining normal hyperplastic gland. There

was no clear line of demarcation between the evidently malignant lesion and the normal gland. In many areas at the periphery of the lesion, there were groups of cells lying in what appeared to be lymph spaces or veins.

Section B (Fig. 6), from a level deeper than in Section A, showed in both the low and high power magnifications many of the features already described for Section A. The adenoma now was more rounded and the capsule was more clearly defined, particularly in the zone of perforation previously described. Increased calcium deposits were noted in the capsule at this point. The large central area of necrosis surrounded by the zone of calcium deposit was still visible. A strikingly wide zone of hyalinized fibrous tissue surrounded the nodule. Many bands of intertwining connective tissue enclosed small and large spaces containing groups of epithelial cells without definite structure and small irregularly formed acini. In the larger spaces one could see thyroid acini of irregular size and shape, some with papillary infoldings of the walls. In many instances there was a reduplication of the lining cells. In one large area there was an abortive attempt to form acini. The nuclei of the epithelial cells were of every size and shape, some containing a scant amount of granular chromatin while others were definitely rich in chromatin or pyknotic (Figs. 7 and 8). In a few instances there were lymphoid and plasma cell accumulations about the epithelial cells imbedded in the connective tissue ground substance. More peripherally, a zone of invasion was recognized in which cords and masses of epithelial cells were seen between connective tissue strands which radiated outwards into the adjacent normal gland.

Section C (Fig. 6), illustrated the findings at a level still deeper than that described for each of the two previous sections. A mere vestige of the primary adenomatous nodule was still recognizable in the central area of calcium deposit enclosed in fibrous tissue. This section passed tangentially through the very periphery of the nodule and, in both the low and high power magnifications, resembled the appearances described for Section B, with the exception that the spaces enclosed in the broad bands of hyaline connective tissue were larger and the contained thyroid tissue was more papillary in structure. There were large irregular acini filled with colloid while others contained granular detritus. The cells lining the acini were of the low cubical type and showed shrunken cytoplasm. The nuclei were strikingly large, irregular in shape, hyperchromatic, often reduplicated and in certain areas there was desquamation of the lining cells into the lumina. Another rather large space in the hyaline stroma was occupied by cells irregularly grouped with scant protoplasm and containing nuclei varying greatly in size and shape. In general, the findings were not unlike those described for Section B.

Pathologic Diagnosis: Scirrhus and papillary adenocarcinoma, occurring in exophthalmic goiter and arising in a papillary carcinoma which was primary in a minute adenoma. Perforation of the capsule of the adenoma by the malignant lesion.

Comment.—The scirrhus and papillary adenocarcinoma occurring in this case of exophthalmic goiter had its origin in a papillary carcinoma which was primary in a minute adenoma. The adenoma had undergone almost complete degeneration. The malignant growth after perforating the capsule of the adenoma had involved the adjacent hyperplastic gland. The scirrhus nature of the growth was readily recognized. Again, except for the fortuitous finding of the adenoma, a diagnosis of carcinoma primary in the hyperplastic exophthalmic gland would have been justified. A follow-up report, dated July 20, 1943, approximately five and one-half years after thyroidectomy, indicated that the patient was in excellent health.

DISCUSSION AND SUMMARY

Nine instances of minute carcinomatous lesions occurring in the diffuse hyperplastic thyroid gland have been carefully studied. The pathologic findings revealed that in three instances, two of which are reported in detail, the lesions were definitely not primary in the hyperplastic gland. They were unmistakably secondary to minute fetal adenomata, and presented all the histologic criteria of malignancy. In several of the remaining cases, the lesions, because of the embryonic character of their epithelium, were strongly suspected of having originated in adenomata. It would appear that carcinoma, even in the relatively rare instances in which it occurs in the hyperplastic thyroid, originates in a preexisting minute adenoma. The question, therefore, arises whether carcinoma is ever truly primary in the hyperplastic thyroid gland.

There are two commonly stated theories concerning the origin of these minute adenomata. According to the first, propounded by Wölfler,[7] and in accordance with the Cohnheim theory of the origin of tumors from congenital "anlagen," the adenoma was thought to arise from the round glandular cells which Wölfler described as occurring in irregular groups both in the thyroid of the newborn and that of the adult. Wölfler believed that they must be considered as embryonal glandular cells which have not been utilized in the formation of the normal thyroid follicles and thus became interacinar in position. He stated, further, that in the highly organized thyroid gland with completely developed acini and high columnar epithelium such interacinous cell groups are usually not discernible. Thus, he thought it was probable that in these instances the undifferentiated cell groups are regularly organized and converted into normal glandular acini. Accordingly, it would seem that the potential of hyperplastic development has exhausted the available undifferentiated cells. Hence, there are no remaining cell groups capable of development into future adenomata. This, on theoretic grounds, could explain the rare coexistence of adenoma and exophthalmic goiter. The second view was expressed by Graham,[8] who, by argument and exclusion, came to the conclusion that, by dedifferentiation or reversion of the follicular cell, a more embryonic type of thyroid epithelial cell from which the adenoma probably arises, is formed. The influences which would cause the thyroid cell to dedifferentiate after its differentiation to the highest functional stage of hyperplastic cell of exophthalmic goiter remain obscure.

I should like to offer the theory that the true adenoma probably has its origin in certain cells which occur in the normal and hyperplastic follicle, and which are known to have the characters of fetal or embryonic cells. They are not uncommonly found singly or in pairs and are interposed between the follicular lining cells of the hyperplastic gland. They can be clearly differentiated from the remaining cells of the follicle by their differences in size and shape and in the nature of the mitochondria which their protoplasm contains. They differ in that they have a rich content

of mitochondria which are rounded, short, filamentous or granular, and resemble fetal or embryonic cells, whereas in the hyperplastic cell of exophthalmic goiter the mitochondria are long, filamentous or spirilliform and fewer in number. Inasmuch as these follicular "fetal" cells are similar in appearance to the cells of the fully developed fetal adenoma they may readily be the ancestral cells of this tumor. According to this view, it is unnecessary to presuppose the dedifferentiation of the highly developed follicular cell. It seems plausible that the follicular "fetal" cells might well predispose to development of carcinoma either primarily or through the intermediate stage of a benign adenoma.

The exciting stimulus for the initial development of cancer either by dedifferentiation of hyperplastic follicular cells or from the fetal-type follicular cell is, of course, totally obscure. One wonders whether carcinoma ever originates in the hyperplastic cell. From the results of studies here reported, it would seem that the hyperplastic cell is probably rarely if ever subject to true malignant degeneration. The undifferentiated fetal cell in contrast to the more highly differentiated hyperplastic cell would seem definitely less removed from a predisposition to malignancy.

It is a common observation that the coexistence of true adenoma and the hyperplastic gland of exophthalmic goiter is strikingly rare. This fact doubtless accounts for the extremely low incidence of carcinoma in exophthalmic goiter. It may well be that even in the few reported cases of malignancy in hyperplastic goiter the malignant neoplasm may well have had its origin in a minute adenoma. In recognized clinical carcinoma involving exophthalmic goiter, it would be impossible to demonstrate the adenomatous origin of the neoplasm because the original adenoma would long have been obscured by the overgrowth by the malignant process. Accordingly, carcinoma arising in a minute adenoma might readily be erroneously considered as primary in the hyperplastic gland. In view of the difficulty in determining the primary tissue, one can never be quite correct in classifying certain specific instances of carcinoma of the thyroid as "adenocarcinoma not arising in adenoma."

The adenoma is essentially an abortive attempt to form normally differentiated tissue. In failing to accomplish this its cells tend to remain fetal in type and the adenoma continues as a precancerous lesion and as an intermediate stage between the original fetal cells and eventual malignant degeneration. The adenoma may grow to a considerable size as a benign tumor and later become malignant, or, as these studies reveal, it may be malignant from its earliest period when virtually submicroscopic in size.

Incidentally, the present study illustrates the futility of supposing that a truly early diagnosis of carcinoma could be made, because there is evidence that these predisposing lesions, which are so small as to be easily overlooked in routine examinations of the excised gland, in reality probably have existed for a long time. This idea is borne out by the dense

fibrosis and even partial calcification seen in a number of the lesions studied. It is interesting to speculate what might have been the outcome had the patients with these lesions described not been operated upon. It would seem that there are many instances in which eventual carcinoma arising in a minute adenoma is prevented by the commonly practiced surgical resections.

CONCLUSIONS

(1) Evidence is submitted indicating that carcinoma apparently primary in (exophthalmic) hyperplastic goiter is, in fact, secondary to malignant degeneration of an intermediate preexisting minute adenoma. It is probable that carcinoma is rarely, if ever, truly primary in the hyperplastic thyroid gland.

(2) Nine instances of incipient carcinomatous lesions occurring in the diffuse hyperplastic thyroid were studied. Pathologic findings revealed that in three of these cases, two of which are reported in detail, the carcinomatous nodule showed a central minute cancerous adenoma. In several of the remaining cases, the origin of the malignant lesions in preexisting minute adenomata was strongly suspected.

(3) The concept of primary carcinoma occurring in the hyperplastic thyroid is not based on firm premises and is likely incorrect.

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CARCINOMA OF THE BREAST*

II—CRITERIA OF OPERABILITY

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WE HAVE RECENTLY PRESENTED[1] in detail the results of treatment in a series of 1040 cases of carcinoma of the female breast seen at the Presbyterian Hospital in New York during the period 1915 to 1934 (inclusive).

In the course of studying this series of cases we were impressed with the frequency with which radical mastectomy had been performed upon far advanced cases, cases which we ourselves today would classify as inoperable. Several of the surgeons who performed many of the operations in the series held to the theory that patients should be given their chance of cure by operation, even though it might be exceedingly small. The practical application of this theory led them to attempt to remove very extensive lesions. This fact makes the series of cases particularly instructive to study from the point of view of determining just which of the various clinical signs of locally advanced carcinoma of the breast are truly indicative of incurability, or to speak more correctly, of inoperability, for operation is the only method by which we can cure breast carcinoma.

In this, as well as in other clinics, there is strong evidence that the improvement in the results of radical mastectomy which has occurred during recent years is due to a large extent to the narrowing of the limits of operability. We are gradually learning that certain types of cases can not be cured even by the most radical operation. But this problem of estimating the true extent of breast carcinoma and of accurately classifying the cases from the clinical evidence alone is a difficult one. We need more detailed data based upon careful and complete clinical descriptions of the disease picture. In studying the Presbyterian Hospital series of cases we have made a special effort to provide these data. The comparatively complete case histories available in this hospital favored this effort, and the good follow-up provided the necessary information as to end-results of operation. The use of the punch-card method of analyzing our data has made it possible to determine the statistical significance as regards operability of the various clinical signs of the extent of the disease, not only individually but in various combinations. A large series of correlations between clinical signs and end-results was easily worked out by this method, and in the present communication we shall present such of these correlations as seem interesting and significant. Miss Dorothy Kurtz, Supervisor of the Presbyterian Hospital Record Room, and an authority on the use of the punch-board method in medical problems, has advised and assisted us in this study.

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Reference to our recent communication dealing with results of treatment in the Presbyterian Hospital series of cases will show that 640, or 61.5 per cent of the total of 1040 patients with breast carcinoma seen in the hospital over the period 1915 to 1934 (inclusive), were treated by radical mastectomy. Within the first five years following operation 146, or 22.8 per cent, of these patients developed local recurrence. At the end of this period 231, or 36.1 per cent, remained free of clinical evidence of carcinoma and were classed as five-year clinical cures.

In the following pages 21 different factors are examined *seriatim*, which have been presumed to be evidences of unfavorable prognostic significance and which were present in women treated by radical mastectomy. In each instance the five-year clinical cure rate is compared with that for the group as a whole. It will be shown that in the case of eight different factors radical operation invariably failed to cure a single case. These factors we consider mandatory contraindications to radical mastectomy. Five other factors, not by themselves categorical contraindications, will be shown to become so when more than one of them is present in the same patient. Finally, it will be shown that some factors popularly supposed to be of very grave import are not as black as they have been painted. Constitutional factors will be considered first, followed by those which may be classified as physical signs of the extent of the disease.

CONSTITUTIONAL FACTORS AFFECTING OPERABILITY

At some future date, when we know much more than we now do about the relationship of somatic type to disease, it may be possible to correlate a variety of constitutional factors with the outlook in breast cancer. Today, however, we are limited to reporting the effects of more prosaic factors such as age and pregnancy-state upon prognosis.

AGE OF THE PATIENT

The most obvious of these constitutional factors is the age of the patient. It has long been recognized by oncologists that neoplastic disease in general is apt to be more malignant when it occurs in young persons. This relationship has been confirmed in breast cancer by many observers, and Taylor[2] has emphasized it in a separate communication on the question. Some surgeons go so far as to decline to operate upon women under the age of 30, who develop breast carcinoma.

In our series the results of radical mastectomy in the different age-groups were as shown in Tables I and II.

These data leave no doubt that radical mastectomy is worth while, even in the youngest patients with breast carcinoma, provided, of course, that the lesion itself is not too far advanced. If the three patients under the age of 30 in our series whose tumor developed during pregnancy or lactation are excluded, as indeed they should be for reasons which we shall shortly demonstrate, the five-year cure rate in the remaining 15 young

TABLE I

RESULTS OF RADICAL MASTECTOMY ACCORDING TO QUINQUENNIAL AGE-GROUPS

Age-Group	No. of Operations	Operative Deaths		5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Under 30	18	0		4	22.2%	4	22.2%
30–34	32	0		8	25.0%	10	31.3%
35–39	68	1	1.5%	23	33.8%	20	29.4%
40–44	121	3	2.5%	28	23.1%	46	38.0%
45–49	121	3	2.5%	28	23.1%	46	38.0%
50–54	100	3	3.0%	21	21.0%	43	43.0%
55–59	68	5	7.4%	17	25.0%	19	27.9%
60–64	58	1	1.7%	12	20.7%	17	29.3%
65–69	35	2	5.7%	3	8.6%	17	48.6%
70+	19	2	10.5%	2	10.5%	9	47.4%
Total	640	20	3.1%	146	22.8%	231	36.1%

TABLE II

RESULTS OF RADICAL MASTECTOMY IN 18 WOMEN UNDER 30 YEARS OF AGE

Record No.	Age	Origin During Preg. or Lact.	Metastases	5-Year Local Recurrence	Outcome
433589	22	No	0	0	Well five years
67803	23	Pregnancy	+	0	Died 4 months
56898	24	No	0	+	Died 25 months
409907	25	No	+	0	Died 39 months
224439	26	Lactation	+	+	Died 9 months
42141	27	No	Not proved	Not known	Living, with metastasis, 9 years
361804	28	No	0	0	Died 27 months
15883	28	No	+	0	Died 59 months
34743	28	No	+	0	Died 29 months
384644	29	No	+	0	Died 9 months
408290	29	No	0	+	Recurrence 59 months. Died 83 months
378962	29	No	+	0	Well 6 years
347901	29	No	+	0	Died 52 months
288630	29	No	+	0	Died 22 months
257685	29	Lactation	+	0	Metastasis sacrum 59 months. Died 111 months.
230452	29	No	+	0	Well until local recur. and met 8 yrs. Died 10 yrs.
67958	29	No	0	0	Well 10 years
50052	29	No	+	+	Died 18 months

patients rises to 37.5 per cent, a figure quite comparable with the cure rate for our series of cases as a whole.

Indeed, when the patients in our series are grouped according to age into broader categories there is surprisingly little difference in the results of operation in the different groups. Table III brings this fact out:

TABLE III

RESULTS OF RADICAL MASTECTOMY IN THREE AGE-GROUPS

Age-Group	No. of Operations	Operative Deaths		5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Under 45	239	4	1.7%	63	26.4%	80	33.5%
45–59	289	11	3.8%	66	22.8%	108	37.4%
60 or over	112	5	4.5%	17	15.2%	43	38.4%
Total	640	20	3.1%	146	22.8%	231	36.1%

The surgeon dealing with breast carcinoma is also interested in the problem presented by patients of advanced age. Armed, as we are today, with methods of preventing and combating shock, we can perform, successfully, extensive surgical procedures upon aged patients upon whom we would not have dared operate previously.

In the present series there were a total of 45 women, age 70, or over, among the 876 primary cases. In 15 of these the carcinoma had progressed beyond the operable stage when they were first seen, while 12 were classed as constitutionally inoperable because of cardiovascular or other associated lesions (seven of these patients not only had inoperable cancer but were also judged constitutionally inoperable). Only four patients, ages 71, 74, 75, and 83, respectively, were denied radical mastectomy on the basis of advanced age alone. Twenty-one were judged suitable for the operation, but two of these refused it. Among the 19 who underwent it the results were surprisingly good. Nine, or almost one-half, were alive and well at the end of five years, and the average length of survival of those who have had no recurrence of their carcinoma has, to date, averaged 87 months. The most noteworthy case is that of a woman who had her radical operation at the age of 78, and today, at the age of 89, is still hale and hearty.

We are led by this evidence to conclude that radical mastectomy is often feasible and worth while in patients in their eighth decade who come with breast carcinoma. Patients in their eighties present a more difficult problem. Even when their general condition is good we have hesitated to perform radical mastectomy. Perhaps we are too cautious. As our experience with surgery on patients in their eighties increases we may learn that radical mastectomy is reasonably safe even in this group. During the past year, however, we have, instead, chosen to carry out simple mastectomy under regional block anesthesia on two patients age 89. In the series of 640 radical mastectomies, which are the subject of the present report, there were none undertaken upon patients in their ninth decade.

In operating upon these elderly patients it is much more important to *avoid* shock than to treat it well after it has developed. Shock has a much higher mortality in them than in younger patients. It becomes, so to speak, irreversible, and death follows from cerebral hemorrhage or cardiac failure.

The degree of decreptitude which the patient shows, and particularly the condition of her cardiovascular system, are, of course, more important than her age in itself in judging her ability to withstand radical mastectomy. While we have repeatedly performed the operation upon patients in their seventies, whose general condition was good, we have decided against attempting it upon some women in their sixties with severe hypertension, for instance. Among the total of 236 primary cases in which radical mastectomy was not performed in the present series there were 24 in which the basis for withholding the operation was the presence of some disease other than carcinoma. All of these had cardiovascular lesions of some type. One patient, in addition, had severe colitis, another, diabetes, and a third, hyperthyroidism.

Certainly these two latter diseases do not, today, in themselves, contraindicate radical mastectomy. We have performed it in a number of patients after these disturbances have been brought under control by appropriate treatment.

Cardiovascular lesions present a more difficult problem. We have placed a good deal of reliance upon the simple functional test of stair-climbing. If a patient has been able to carry on a certain amount of daily physical activity which includes climbing even a single flight of stairs without acute distress we have judged her able to withstand radical mastectomy. In patients with hypertension we attempt to choose an anesthetic that neither depresses nor elevates the blood pressure unduly. Dr. Apgar, Director of the Department of Anesthesia in the Presbyterian Hospital, prefers nitrous oxide anesthesia for such patients, and warns against the use of avertin as a basic anesthesia for them because of its well known tendency to depress the blood pressure. In passing, it might be noted that avertin-nitrous oxide anesthesia is our favorite for these long breast dissections, provided there is no special contraindication to it.

PREGNANCY AND LACTATION

In view of the great stimulus to growth that the breast receives with the onset of pregnancy, and its active metabolism during lactation, it is but natural that a carcinoma developing during this period should be exceptionally malignant. This has, indeed, been the experience of all surgeons who have faced the problem. Yet there is a diversity of opinion as to the degree to which the malignancy of breast carcinoma is increased by pregnancy and lactation, and a corresponding lack of agreement as to whether or not pregnancy should be interrupted, and whether radical mastectomy should or should not be performed. In recent years data regarding this question have been presented by Bromeis,[3] from the University Surgical Clinic, at Tübingen, and by Harrington,[4] from the Mayo Clinic. Neither of these authors, however, tell us how many lasting cures were achieved in their clinics—they write only of survivals.

In the Presbyterian Hospital series of 876 primary cases there were 29 in which the breast carcinoma developed during pregnancy or lactation. In 20 of these women radical mastectomy was carried out (Table IV). There were no permanent cures. One patient remained well until six years after operation, when she developed local recurrence and pulmonary metastases, and died after another 18 months.

The results look better when expressed in terms of five-year survival, as Harrington presented them. Three, or 15 per cent of our 20 patients, were alive five years after operation, although all three succumbed later. Harrington reported the results of operation in a total of 99 women in whom breast carcinoma occurred during pregnancy or lactation. Thirteen of them, or 13.2 per cent, survived for at least five years. Thirty-two of his patients were traced 20 years after operation, and only one was found to have survived.

Another way of estimating the comparative malignancy of carcinoma of

the breast developing during pregnancy or lactation is in terms of the frequency of axillary metastasis. In our series of 20 cases that were operated upon 19, or 95 per cent, were found to have axillary involvement. The incidence of axillary involvement in our total series of 640 breast carcinoma was, on the other hand, 61.7 per cent. In Harrington's series of 99 cases of breast carcinoma developing during pregnancy or lactation the axillary nodes were found to be involved in 84.8 per cent, as compared with an incidence of 61.6 per cent in his series as a whole.

TABLE IV

CARCINOMA OF THE BREAST DEVELOPING DURING PREGNANCY OR LACTATION AND TREATED BY RADICAL MASTECTOMY

Case No.	Age	Time of Appearance	Axillary Metastases	5-Year Local Recurrence	Sites of Metastases	Follow-up
20616	37	6 mos. preg.	+	+	Other breast	Died 13 mos. postop.
49799	43	16 mos. before preg.	+	+	Bones	Died 25 mos. postop.
59522	31	3 mos. lact.	0	+	Lungs	Died 41 mos. postop.
67256	33	15 mos. lact.	+	0	None	Died, lead therapy, 5 mos. postop.
67379	32	9 mos. lact.	+	0	Lungs and bones	Died 15 mos. postop.
67803	23	Beginning of preg.	+	0	Other breast and bones	Died 4 mos. postop.
71423	33	1 mo. preg.	+	0	Lungs	Died 8 mos. postop.
80985	32	4 mos. preg.	+	0	Bones	Died 26 mos. postop.
81542	38	16 mos. lact.	+	0	Liver	Died 5 mos. postop.
224439	26	5 mos. lact.	+	+	Lungs and bones	Died 9 mos. postop.
258421	34	30 mos. lact.	+	0	Bones	Died 11 mos. postop.
350471	36	2 mos. before preg.	+	+	Bones	Died 17 mos. postop.
375570	37	10 mos. before preg.	+	0	Lungs	Died 19 mos. postop.
407734	38	48 mos. lact.	+	+	Other breast and lungs	Died 8 mos. postop.
415597	42	6 mos. lact.	+	0	Bones	Died 43 mos. postop.
64106	38	1 mo. before preg.	+	0	Lungs	Local recur. and met. 6 yrs. postop. Died 7½ yrs. postop.
257685	29	16 mos. lact.	+	0	Bones and ovaries	Recur. 59 mos. postop. Died 111 months postop.
57379	31	7 mos. lact.	+	0	Supraclav. node	Died 12 mos. postop.
73673	44	7 mos. preg.	+	0	Lungs	Recurrence 50 mos. postop. Died 66 mos. postop.
232863	40	7 mos. lact.	+	0	Lungs, bones and liver	Died 33 mos. postop.

These several types of evidence suggest to us that carcinoma of the breast developing during pregnancy or lactation is so malignant that surgery can not cure it often enough to justify this method of treatment. We prefer to classify these patients as *categorically inoperable*, and to treat them palliatively with radiation.

When pregnancy occurs following the successful removal of carcinoma of the breast it has no special unfavorable prognostic significance. If the carcinoma has been entirely removed the growth stimulus of pregnancy has no effect. If, on the other hand, a focus of carcinoma cells persists somewhere in the patient's body their resurgence may, of course, be hastened by a subsequent pregnancy, but the patient would have been doomed eventually anyway.

so that the ultimate cure rate remains unaltered by the incident of pregnancy. Seven of our 640 patients treated by radical mastectomy subsequently went through one or more pregnancies. In this small group of seven the five-year cure rate was 42.9 per cent, approximately the same as in our patients who did not subsequently become pregnant. Harrington's experience was similar. Subsequent pregnancy occurred in 59 of his patients, and five-year survival rate was 78.2 per cent in the group.

Influenced by these facts it has been our custom not to deny pregnancy to patients who have satisfactorily gone through radical mastectomy and appear to have a favorable prognosis, *i.e.*, no axillary metastases or other unfavorable features.

PHYSICAL SIGNS OF EXTENT OF DISEASE WHICH EFFECT OPERABILITY

Not all of the many physical signs which breast carcinoma produces have a bearing upon operability. Thus, dimpling of the skin, deviation and retraction of the nipple, and distortion of the outline of the areola, which are among the most common signs of the disease, are important in diagnosis but, in themselves, they have no bearing upon the question of operability, which we are here discussing, for the patients with them are always operable unless some other physical sign makes it necessary to class them as inoperable.

But the significance of certain other physical findings in breast carcinoma, such as ulceration and edema, is not generally agreed upon. There has been a dearth of satisfactory and detailed data regarding them. It is to these physical signs of problematic prognostic significance that we will devote our attention.

THE SITE OF CARCINOMA IN THE BREAST

The site of the tumor in the breast is one of these factors which comes first to mind. The relationship of the site of the tumor to the results of radical mastectomy in our series of cases is shown in Table V.

TABLE V

RESULTS OF RADICAL MASTECTOMY
ACCORDING TO THE SITE OF THE CARCINOMA IN THE BREAST

Site in Breast	No. of Operations	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Upper outer quadrant	277	51	18.4%	118	42.6%
Upper inner quadrant	78	17	21.8%	27	34.6%
Center	74	22	29.7%	24	32.4%
Lower outer quadrant	51	8	15.7%	17	33.3%
Lower inner quadrant	28	11	39.3%	6	21.4%
Upper half	47	10	21.3%	14	29.8%
Lower half	15	3	20.0%	5	33.3%
Outer half	35	15	42.9%	7	20.0%
Inner half	5	3	60.0%	2	40.0%
Entire breast	15	5	33.3%	2	13.3%
Not stated	15	1	6.7%	9	60.0%
Total	640	146	22.8%	231	36.1%

These data confirm the general experience that the upper outer sector of the breast is the one most frequently affected by the disease. Moreover, the best results of operation are obtained with tumors in this same sector. Perhaps this is because surgeons who perform the standard radical operation, and close their wounds, are able to remove the tumor with a wider margin of uninvolved surrounding tissues when it is situated in the upper outer sector than when it is in any other part of the breast.

There is one situation in which breast carcinoma occasionally develops which is not listed in our table, namely, the inframammary region. We are today familiar with this form of breast carcinoma, but it was not identified as a special type of the disease by most of the surgeons who, in years gone by, wrote the descriptions of the cases here reported. We are unable, therefore, to present data regarding it.

It is our impression, however, from the patients with carcinoma in the inframammary fold which we have personally observed, that this form of the disease is a particularly favorable one. Patients are apt to detect a tumor in this situation early, because it is not hidden in the depths of surrounding fatty breast tissue but stands out in sharp relief along the fold where the fascia covering the breast fuses with the fascia covering the abdominal wall.

From the standpoint of operability, there is no site in the breast in which carcinoma can be deemed beyond the scope of surgical attack. When the entire breast is involved the results are poor, but this question of the significance of the extent of the local disease is better discussed on the basis of actual measurements of the tumor. It is the next factor which we shall discuss.

THE SIZE OF THE BREAST TUMOR

The importance of making careful measurements, preferably in centimeters, of all breast tumors can not be too strongly emphasized. Fortunately, such measurements were available in the great majority of our cases. The correlation between results of radical mastectomy and the size of the tumor in our series is shown in Table VI.

TABLE VI

RESULTS OF RADICAL MASTECTOMY ACCORDING TO THE SIZE OF THE BREAST TUMOR
(*Clinical Measurements*)

Size of Tumor	No. of Operations	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Under 30 mm.	82	11	13.4%	51	62.2%
30 to 59 mm.	256	50	19.5%	110	43.0%
60 mm., or over	222	74	33.3%	43	19.4%
Size not stated	80	11	13.8%	27	33.8%
Total	640	146	22.8%	231	36.1%

These data indicate, as might be expected, that the prognosis becomes worse as the size of the tumor increases. Local recurrence is more frequent and the five-year clinical cure rate is lower.

But large size, alone, is no contraindication to operation. Even the largest breast carcinomata, if they do not exhibit any unfavorable feature other than their large size, can often be cured by surgery. Table VII illustrates this point. In it are shown the results of operation in 19 cases in which the primary tumor in the breast measured ten centimeters, or more, in diameter. Cases which we have classified as *categorically inoperable* for several reasons, and which we will discuss in detail later on in this report, have not been included in this table.

TABLE VII

RESULTS OF RADICAL MASTECTOMY

CASES IN WHICH THE TUMOR MEASURED TEN CENTIMETERS, OR MORE, IN DIAMETER

(*Clinical Measurements*)

(*Categorically Inoperable Cases Excluded*)

Physical Findings	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
10 cm., or more, tumor *only*	12	2	16.7%	3	25.0%
10 cm., or more, tumor *with** signs of locally advanced disease	7	2	28.6%	1	14.3%
Total	19	4	21.1%	4	21.1%

The size of the breast tumor bears a general relationship to its duration, or rather to the duration which the patient alleges. This relationship is shown in Table VIII. In this table the measurements used are those made by the pathologist after the specimen has been cut. It is noteworthy that some tumors remain small even after they have been present for a long time.

TABLE VIII

RELATIONSHIP OF THE SIZE OF THE TUMOR (PATHOLOGIC MEASUREMENTS) TO ITS DURATION

Size of Tumor	No. of Operations	Duration				
		Under 1 Mo.	1 to 5 Mos.	6 to 11 Mos.	1 Yr. +	Not Stated
Under 20 mm.	64	18	26	9	9	2
20–49 mm.	272	46	98	43	60	25
50 mm. +	182	17	68	43	46	8
Not stated	122	19	44	24	25	10
Total	640	100	236	119	140	45

Although the probability of finding axillary metastases increases as the breast tumor enlarges, it is distressing to note that even in the group of

* In this, and in the following tables dealing with the prognostic significance of other individual features of breast carcinoma, *the signs of locally advanced disease* referred to are the ones which we have found from our data to have the gravest prognostic import. They include ulceration of the skin, edema of the skin, fixation of the breast tumor to the chest wall, axillary lymph nodes measuring 2.5 cm., or more, in transverse diameter, and fixation of the axillary nodes to the chest wall or overlying skin.

cases with the smallest tumors (under 20 mm. in diameter) the incidence of axillary metastasis is large, to be exact 43.8 per cent. These data are shown in Table IX. Again the measurements used are those made by the pathologist.

TABLE IX

RELATIONSHIP OF THE SIZE OF THE TUMOR (PATHOLOGIC MEASUREMENTS) TO AXILLARY METASTASIS

Size of Tumor	No. of Operations	Axillary Metastasis		Axillary Nodes Not Examined
		No.	Per Cent	
Under 20 mm.	64	28	43.8%	0
20–49 mm.	272	151	55.5%	7
50 mm. +	182	135	74.2%	3
Not stated	122	71	58.2%	8
Total	640	385	60.2%	18

MULTIPLE TUMORS IN ONE BREAST

Pathologic study not infrequently reveals that breast carcinoma exists in multiple foci in the affected breast, particularly in the relatively advanced cases, but these multiple tumors are not often detected clinically. We do not refer, of course, to satellite tumor nodules in the skin but to separate foci of carcinoma within the breast tissue itself. In our series there were only twelve such cases diagnosed clinically among the 640 in which radical operation was performed. It is probable that more careful palpation would reveal them more often.

Although our group of cases is small after the *categorically inoperable* ones have been excluded, Table X shows that the results of operation were relatively good in the 12 cases in which the multiple nature of the disease in the affected breast was the only prognostic factor that had to be considered. In the three cases in which there were multiple tumors and, in addition, other signs of locally advanced disease there were, however, no cures.

TABLE X

RESULTS OF RADICAL MASTECTOMY

CASES IN WHICH THERE WERE MULTIPLE TUMORS IN ONE BREAST

(Clinical Diagnosis)

(Categorically Inoperable Cases Excluded)

Physical Findings	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Multiple tumors *only*	9	3	33.3%	4	44.4%
Multiple tumors, *with* signs of locally advanced disease	3	1	33.3%	0	
Total	12	4	33.3%	4	33.3%

LOCAL ELEVATION OF SKIN TEMPERATURE

Our personal study of breast tumors has convinced us that careful comparison of the skin temperature over the tumor with that of a corresponding

skin area on the opposite breast will often show that the skin over the tumor is warmer. Although this sign is most frequently found in carcinoma we have observed it in a variety of types of benign tumors and we do not attach any special diagnostic significance to it.

We are unable to present any data regarding the prognostic significance of elevation of skin temperature because most of the surgeons who, in years gone by, wrote the descriptions of the cases reported in this series did not make any note of this sign.

REDNESS OF THE SKIN

Redness of the skin is sometimes a striking feature of breast carcinoma. While in the far-advanced cases it is seen as the result of actual involvement of the skin by the disease, in earlier ones it may develop merely as part of an inflammatory-like reaction which some carcinomata induce in the tissues which surround them.

TABLE XI

RESULTS OF RADICAL MASTECTOMY
CASES IN WHICH THERE WAS REDNESS OF THE SKIN
(Categorically Inoperable Cases Excluded)

Clinical Group	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Redness *only*	23	6	26.1%	8	34.8%
Redness, *with* signs of locally advanced disease	30	13	43.3%	6	20.7%
Total	53	19	35.8%	14	26.4%

Table XI shows the results of radical mastectomy in the cases in the present series in which redness was noted, excluding the ones classified by us as *categorically inoperable*. Among these latter is the group of so-called "inflammatory" carcinomata in which redness is a prominent feature of the clinical syndrome. It will be seen from this table that redness occurring alone does not imply a bad prognosis. When it occurs with other signs of locally advanced disease, however, the outlook is considerably poorer.

INVOLVEMENT OF THE SKIN

Involvement of the skin over the tumor, as we have used it in the present classification, refers to those cases in which the skin over the tumor has become fixed and immovable. This is a clinical and not a pathologic criterion. It does not include the cases in which this involvement has progressed to the point of ulceration; these form a separate group which we shall discuss subsequently.

Table XII shows the results of radical mastectomy in these cases with skin involvement, excluding the ones classified by us as *categorically inoperable*. From this table it would appear that skin involvement occurring alone

TABLE XII

RESULTS OF RADICAL MASTECTOMY

CASES IN WHICH THERE WAS INVOLVEMENT OF THE SKIN

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Skin involvement *only*	21	6	28.6%	6	28.6%
Skin involvement, *with* signs of locally advanced disease	44	11	25.0%	8	18.2%
Total	65	17	26.2%	14	21.5%

does not imply a bad prognosis, although when it occurs with other signs of locally advanced carcinoma the percentage of cures decreases.

ULCERATION OF THE SKIN

Ulceration of the skin over a breast tumor is a sign that surgeons know well, and most of them have learned that it does not necessarily mean that the case is hopeless.

TABLE XIII

RESULTS OF RADICAL MASTECTOMY

CASES IN WHICH THERE WAS ULCERATION OF THE SKIN

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Ulceration *only*	9	1	11.1%	2	22.2%
Ulceration, *with* other signs of locally advanced disease	14	4	28.6%	1	7.1%
Total	23	5	21.7%	3	13.0%

Our data, as shown in Table XIII, bear out the truth that ulceration of the skin *occurring alone* does not indicate an unusually bad prognosis. When it occurs together with other signs of locally advanced disease, however, the outlook is indeed poor; in our series the cure rate for such cases was only 7.1 per cent. It should be noted that the cases classified by us as *categorically inoperable* have been excluded from this table.

(*To be continued*)

IMMEDIATE EFFECTS ON RENAL FUNCTION OF THE ONSET OF SHOCK DUE TO PARTIALLY OCCLUDING LIMB TOURNIQUETS*

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In a review of the status of the shock problem, Wiggers (1942) has referred to the lack of quantitative knowledge which would point to the presence of vasoconstriction sufficient to increase greatly resistance in important visceral vascular beds or, by its intensity and persistence, great enough to lead to capillary damage. Clinical observations testify to a slowing of peripheral blood flow and contraction of cutaneous vessels during the early stages of shock and quantitative measurements have confirmed this (Freeman, Shaw and Snyder, 1936, and Bakdes, Herrick, Essex and Mann, 1941). Precise information as to visceral vascular changes was largely lacking until Page and Abell (1943) directly observed mesenteric arteriolar vasoconstriction during the onset of shock. The demonstration of a concurrent and intense renal vasoconstriction would signify an increase in vascular resistance in another and a very large set of vessels since the kidney normally receives some 20 per cent of the cardiac output in the dog (Mason, Blalock and Harrison, 1938, and Levy and Blalock, 1937), and rather more in man (Smith, 1939). Fortunately, this demonstration may be quantitatively made by applying the methods and principles of Van Slyke, Rhoads, Hiller and Alving (1934), and of Smith, Goldring and Chasis (1939). The deficit in information to which Wiggers referred may thus be overcome.

Changes of renal blood flow and function during shock are of current interest also, since they may in a measure explain the pathogenesis of renal failure in "traumatic anuria" ("crush syndrome"). It was with reference particularly to this problem that the work here reported was begun. Briefly, the present report consists of a description of the variations of renal hemodynamics and function which may occur during the onset of shock in anesthetized dogs after renal denervation, and after splenectomy, and during the transfusion of blood. The choice of partially occluding limb tourniquets as a method of producing shock was made because of its simulation of the conditions under which clinical traumatic anuria may occur, and because, in contrast to many procedures, it permits continuous observation of systemic changes.

METHODS

Our observations were made during 14 experiments upon dogs anesthe-

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tized with sodium pentobarbital (Lilly) given in a dose of 30 mg. per kilo of body weight.[1] In some experiments small additional doses of anesthetic were given to maintain an even depth of anesthesia. Two experiments were undertaken in otherwise normal uninephrectomized dogs with one subcutaneously explanted kidney (method of Page and Corcoran, 1940), both operations having been performed three years before. Blood was transfused in one of these, and acacia solution given the other. Two experiments were made in a normal dog not treated by transfusion and two in two normal dogs treated by transfusion. Blood was also given during an experiment upon a dog suffering from renal hypertension (method of Page, 1939). Observations were made in one dog whose legs were firmly wrapped in plaster encasements. Six experiments were done in dogs both of whose kidneys had been denervated 10 to 14 days before the experiment. Splenectomy had been performed in five of these at the time of renal denervation, and these five dogs were given blood during the experiment, while the non-splenectomized subject was treated by infusion of acacia. The grouping of the experiments is shown in Table I.

TABLE I

Type of Experiment	No. of Experiment
A. Normal dogs:	
(a) Nontransfused, one with acacia infused	1, 2, 3
(b) Transfused	4, 5, 6
B. Dogs with denervated kidneys:	
(a) Splenectomized, blood transfused	7, 8, 9, 10
(b) Nonsplenectomized, acacia infused	11
C. Other experiments:	
(a) Renal hypertension	12
(b) Legs wrapped in plaster encasements	13
(c) Collapse not relieved by transfusion	14

In outline, each experiment consisted of (1) a control period of some 30 minutes of observation, following which (2) partially occluding limb tourniquets were applied. The observations were continued for about four hours when (3) the tourniquets were removed and the experiment continued for another 80 minutes or more. Some of the animals were sacrificed and examined at the end of this time, but the majority died 8 to 14 hours after the application of the tourniquets. One animal was allowed to recover and the experiment repeated. The blood which was given was cross-matched and freshly drawn from a donor into a vacuum flask containing sodium citrate solution. It was given to the recipient by intravenous infusion started before the release of tourniquets. The tourniquets consisted of stout cord, and were so applied at the junction of thigh and body that a slow arterial inflow persisted for a time. The legs swelled for an hour or more after

[1] A study now in press (Corcoran and Page, Amer. J. Physiol., 1943) establishes that anesthesia was not the cause of the effects here reported, except possibly in Experiment 14.

their application, when swelling ceased, to begin again after the cords were released by cutting them free. Blood pressure was measured by a mercury manometer connected to the cannulated carotid artery. The arterial pressure usually rose immediately after application of the tourniquets and fell slowly, although not to "shock levels" while they were in place. Blood pressure fell abruptly when the cords were cut, but soon returned to nearly the previous level. Following this, the pressure fell slowly to hypotensive levels during the ensuing hours. The aim of blood transfusion in these experiments was to maintain arterial pressure at approximately normal levels; blood was, therefore, given slowly while the tourniquets were in place, rapidly immediately after their release, and then again more slowly. The course of the shock which follows this procedure in dogs is described in detail by Taylor and Page (1943).

The observations made during the experiments include the renal clearances of diodrast and inulin, urine volume, arterial pressure and hematocrit index (method of Wintrobe). The proportions of diodrast and inulin removed by the kidneys were observed by sampling renal venous blood in the dogs with subcutaneously explanted kidneys. From these proportions (renal extraction ratios) and the plasma clearances, total renal blood and plasma flows were calculated. The levels of total plasma protein were measured in an experiment upon a normal dog. Page (1943) had demonstrated during shock the development of a substance in plasma which constricts the isolated perfused vessels of a rabbit's ear which, pending identification, he has termed "peripheral vasoconstrictor substance." Measurements of this kind were made in seven of the experiments.

For the measurement of clearances, a solution containing diodrast and inulin and 2 per cent of sodium sulfate in physiologic saline solution was infused intravenously, and the rate of infusion varied to maintain the plasma concentrations of diodrast-iodine at 1 to 5 mg. per 100 cc., and of inulin at 30 to 60 mg. per 100 cc. A "priming" dose of the infusion fluid was given 30 minutes before the start of the experiment, and the infusion continued at a rate of 2 cc. per minute or less. Diodrast-iodine was determined in plasma and urine by the method of Corcoran and Page (1943), which utilizes the colorimetry proposed by Flox, Pitesky and Alving (1942). Inulin determinations were done by the method of Corcoran and Page (1939). A soft rubber retention catheter was inserted and the urine collected by careful bladder washing and compression. Urine volume was calculated from the excess volume of urine ± washing fluid. This method of estimating urine volume is, of course, not precise at low levels of urine flow and over short period of collection, although it suffices to demonstrate large changes. However, during the experiments, the periods of collections were prolonged during oliguria, so that the measurements may be accepted as approximating closely the rate of urine secretion. The determination of plasma protein content was made by an adaptation of the method of Kingsley (1942) to the Evelyn photo-electric colorimeter.

RESULTS

A. Normal Dogs.—(a) Nontransfused. 1. Effects of Tourniquet Application: The courses of these experiments (Nos. 1, 2 and 3) are summarized in Chart 1, in which the variations observed are averaged as percentage of change from the control levels. The mean duration of tourniquet application was 215 minutes. During the first 15 minutes the plasma clearances de-

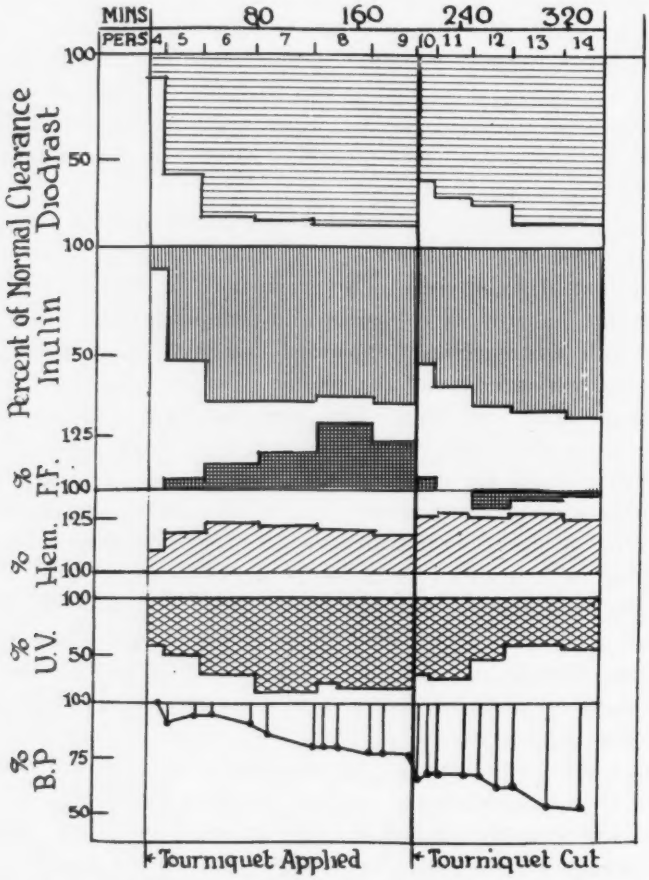

CHART 1.—Means of percentile variations from control levels of diodrast clearance, inulin clearance, filtration fraction (F. F.) hematocrit index (Hem.) urine volume, (U. V.) and blood pressure (B. P.) induced by application and release of partially occluding limb tourniquets in three normal dogs. Abscissa: mins. = minutes from application of tourniquets; pers. = periods of urine collection.

creased by 12 per cent; decreases to about 45 per cent occurred during the next 30 minutes and were followed by further decreases to approximately 25 per cent, at which levels they were maintained. Filtration fraction rose to range between 112 and 131 per cent of the control after the first 15 minutes because of a greater depression of diodrast than inulin clearance. Urine volume was depressed to from 13 to 28 per cent of the control level. Arterial pressure was not altered at first, but after 15 minutes fell slowly

to reach 75 per cent of the control level at the time the tourniquets were released. Hematocrit index increased immediately after application of the tourniquets by 8 per cent, and reached 122 per cent of the control after 45 minutes. The blood loss from sampling in Experiments 1 and 2 was about 60 cc., including that taken during control periods.

The observations in Experiment 3, upon a dog with a single subcutaneously explanted kidney are of especial interest since they provide means of assessing the significance of the clearance changes observed in nonexplanted dogs. Briefly, application of tourniquets did not significantly alter diodrast extraction ratio, which was depressed by only 5 per cent during the whole time; on the other hand, the extraction ratio of inulin was doubled. The fact that diodrast extraction ratio was maintained near control level (0.77) while plasma diodrast clearance fell to about 20 per cent of the control level, indicated that the change in clearance was the result of decreased renal blood flow. Inulin clearance was not as severely depressed because the inulin extraction ratio rose in proportion to the filtration fraction. Plasma total protein decreased from 5.8 to 5.3 Gm. per 100 cc. during the tourniquet application. Total blood loss due to sampling during this time was 190 cc. In spite of this loss, hematocrit index increased from 41 to 47 per cent.

2. Tourniquet Release: Release of the tourniquets caused a sharp fall in arterial pressure for about one minute, after which pressure was restored but at a lower level than before. In two of the three experinments the plasma clearances of diodrast and inulin nevertheless increased. Filtration fraction fell in all three. Urine volume remained low. Hematocrit index was increased. Release of the tourniquets was followed by a slight initial fall in clearances in Experiment 3, which was maintained for about 15 minutes after the cords were cut, when these values fell precipitously. These changes in the clearances were associated with marked changes in diodrast extraction ratio which, in the four periods of observation, yielded values successively of 0.72, 0.68, 0.69, and 0.50. Inulin extraction was maintained at the high level reached during the presence of tourniquets until the last of these periods, when it was observed at zero as the arterial pressure fell to 60 mm. Hg.

The duration of tourniquet application was 191 minutes in Experiment 1, and the dog recovered after the experiment. Experiment 2 was undertaken upon this dog nine days later, and the tourniquets applied for 210 minutes. Death ensued eight hours after beginning the experiment. Duration of application was 245 minutes in Experiment 3, and death occurred 11 hours after beginning the experiment. That renal function was not long affected by the severe changes which developed during Experiment 1 is shown in the clearances of diodrast and inulin were, respectively, 170 and 53 cc. per minute in the control periods of Experiment 1 and 163 and 54 cc. per minute at the start of Experiment 2.

Normal Dogs.—(b) Transfused. 1. Effects of Tourniquet Application: The observations made in this group of three dogs are summarized in Chart

2. Blood was given intravenously starting about 90 minutes after tourniquet application, so that arterial pressure fell by only about 12 per cent. In spite of this partial maintenance of blood pressure, the clearances of diodrast and inulin fell in the manner observed in the first group, and so remained during the first 50 minutes of transfusion, after which the clearances rose to about 50 per cent of normal. Whereas the decrease of clearances had been associated with increased filtration fraction, and oliguria, the subsequent

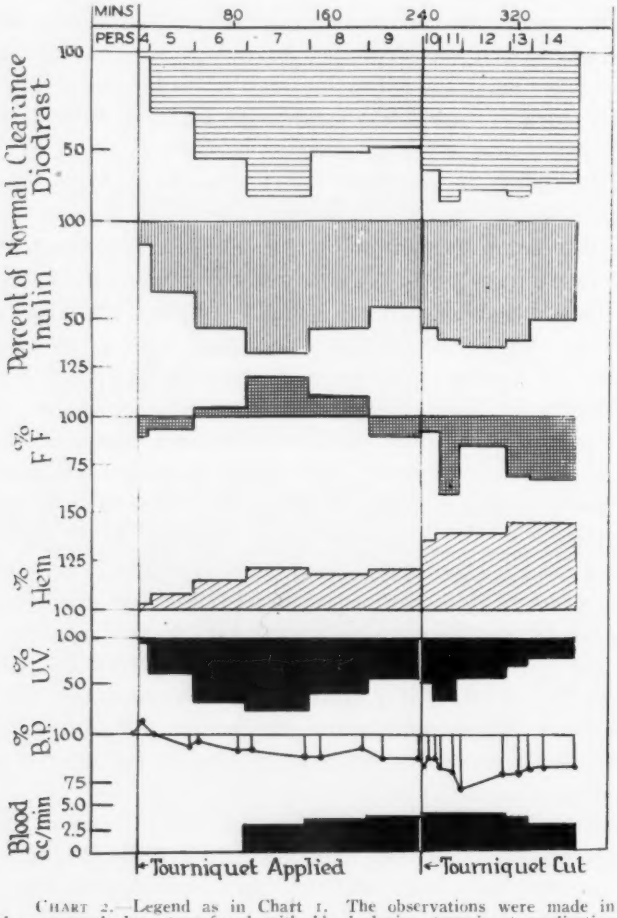

CHART 2.—Legend as in Chart 1. The observations were made in three normal dogs transfused with blood during tourniquet application and release. Duration and rate of transfusion shown in blocked area as, "Blood, cc. per min."

increase was accompanied by a fall in this value and an increase in urine flow. Hematocrit ratio, which had risen before transfusion, was maintained during it. "Peripheral vasoconstrictor substance" was measured in two dogs (Dogs 4 and 6) and shown to appear in the blood in increased amounts after application of tourniquets. The subject of Experiment 6 was one of the two dogs with subcutaneously explanted kidneys, as in the similar dog

(Dog 3) the presence of the tourniquets did not alter the renal extraction ratio of diodrast which was maintained at the control level of 0.68, during a fall of diodrast clearance to 30 per cent and a restoration by transfusion to 60 per cent of the control level. The levels of renal plasma flow, therefore, varied in parallel with those of plasma diodrast clearance. Unlike Experiment 3, the fall of clearance was not associated with a marked increase in inulin extraction ratio or in filtration fraction. This was because the greater decrease in systemic arterial pressure prevented the development of increase in intraglomerular pressure by efferent arteriolar constriction.

2. Tourniquet Release: The transfusion of blood during and after the tourniquet release failed to prevent a fall in the clearances in the subsequent observations, although it did maintain arterial pressure approximately at the level which was previously obtained. Filtration fraction and urine flow remained unchanged, the latter at about 50 per cent of the control level. The hematocrit index rose sharply to a maximum of 145 per cent of the control in the group. In Experiment 6, as in Experiment 3, diodrast extraction ratio fell after tourniquet release to successive levels of 0.55, 0.58, 0.58 and 0.65. Clearance and renal plasma flow were simultaneously depressed in spite of a well maintained arterial pressure. Inulin extraction ratios increased to levels ranging about 0.35 and, as a result, the decrease of inulin clearance was less marked than that of diodrast and filtration fraction increased. "Peripheral vasoconstrictor substance" increased greatly in the blood of this dog just before transfusion and, although at a slightly lower level, remained increased during the experiment, in which, in all, 700 cc. of blood were given. One dog of this group (Dog 5) died 12 hours after the experiment, and the other two were sacrificed at its completion.

B. *Renal Denervation.*—(a) Splenectomy. Transfusion. 1. Effects of Tourniquet Application: The results of four experiments are recorded together in Chart 3. As in the previous two groups, the clearances and the level of arterial pressure were not at first affected by application of tourniquets, but began to fall after about 15 minutes. But, in contrast, they fell only to levels of about 50 per cent of the control and no dog in the group showed the severe fall of clearance (to levels of 20 or 25 per cent of control) which characterized the nondenervated groups of dogs. Filtration fraction rose as the clearances began to decrease, but was later restored to a normal level. Arterial pressure fell by about 18 per cent in spite of slow transfusion of blood as in the nondenervated transfused series (A.—b). Urine volume was depressed roughly in proportion to clearance. Unlike the nonsplenectomized dogs, this group did not show an increase of hematocrit index.

2. Tourniquet Release: The transfusion was speeded as the tourniquets were released and arterial pressure rapidly restored to the level (83 per cent of control) which presented before they were cut. Probably because of hypotension, the clearances fell at first to about 20 per cent of the control and rose to 50 per cent, being ultimately brought nearly to the control level. Hematocrit ratio now began to rise and the increase continued after the

transfusion was discontinued. Urine volume, which had fallen only slightly after release of the cords, rose to exceed the control level when pressure was restored towards the control level.

Two dogs in this group died at 10 and 12 hours after the start of the experiment, while two were sacrificed at its conclusion.

(b) Splenectomy. Nontransfused. Delayed Infusion of Acacia: Only one such experiment was satisfactorily completed. The presence of the

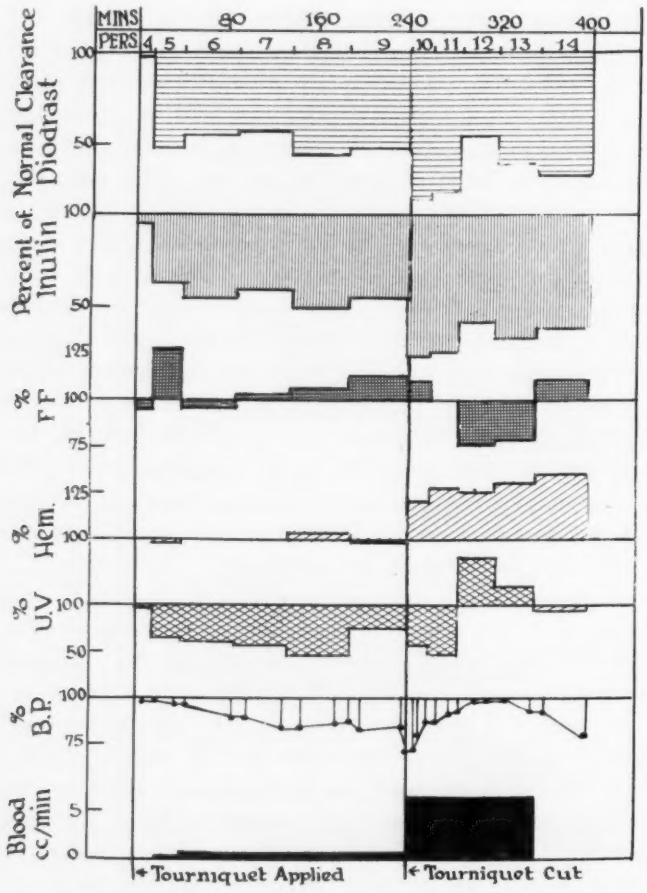

CHART 3.—Legend as in Charts 1 and 2. Observations made in four dogs previously subjected to renal denervation and splenectomy.

tourniquets caused a fall in clearance levels only to about 70 per cent of the control. During this time filtration increased and urine flow was greatly depressed. Arterial pressure reached a minimum of 60 per cent of the control just before release of the tourniquets when they had been on for 250 minutes. The hematocrit index reached 134 per cent of the control immediately after application of the tourniquets and fell slowly afterwards. Re-

lease of the tourniquets caused a sharp fall in arterial pressure to 43 per cent of the control and a subsequent rapid rise to 50 per cent, *i.e.*, 67 mm. Hg. During this time the clearances fell to 13 and 1 per cent of the control levels, and urine flow almost ceased, while the hematocrit index rose sharply to 154 per cent of control. A 6 per cent solution of acacia was then given at a rate of nearly 20 cc. per minute for 26 minutes and the arterial pressure brought to 90 per cent of normal. During this time the clearances rose rapidly, only to fall again with arterial pressure when the infusion was stopped. Hemoglobinuria developed during these observations, and death occurred ten hours after the start of the experiment.

C. *Other Experiments.*—(a) Renal Hypertension: One experiment was undertaken in a dog suffering for one year from mild hypertension due to bilateral perirenal application of silk (Page, 1939). As in normal dogs, the plasma clearances decreased after application of tourniquets to reach about 30 per cent of the control, when pressure had fallen, by 26 per cent, to 152 mm. Hg. Transfusions of blood then rapidly restored the level of arterial pressure nearly to the control, although the plasma clearances remained depressed by about 20 per cent. The hematocrit index had meanwhile risen to about 150 per cent of the control, so that assuming that plasma diodrast clearance is equivalent to renal plasma flow, renal plasma flow was depressed while renal whole blood flow was actually increased. Release of the tourniquets did not further lower arterial pressure which increased to the control level as transfusion continued, as did the plasma clearances of diodrast and inulin. The hematocrit index remained high, so that apparent total renal blood flow further increased above the normal as was also urine flow. It is noteworthy that measurements of "peripheral vasoconstrictor substance" showed no development of this material in the blood during the experiment.

(b) Effect of Limb Encasements: Snugly fitting plaster encasements were applied to the legs of one dog from foot to thigh before the control periods. That such a procedure does not affect clearance is shown in the fact that the values obtained during the control periods of the experiment were identical with those previously observed in this dog when conscious. The course of this experiment is shown in Table II, from which it will be seen that application and release of the tourniquets under this condition did not alter renal function.

(c) In Experiment 14 upon an apparently normal dog, arterial pressure began to fall from the control of 133 mm. Hg. 40 minutes after application of tourniquets, and continued to fall in spite of rapid intravenous transfusion of blood, and was only temporarily stabilized at 100 mm. Hg. after the infusion of 600 cc. of blood (roughly, 0.6 of this animal's probable blood volume). The fall in pressure was associated with a severe reduction of renal clearances, which were restored only to 50 per cent of the control when the pressure was brought to 100 mm. Hg., while oliguria continued. After 92 minutes, the experiment was discontinued and the tourniquets released. The dog died 15 hours from the start of the experiment.

TABLE II

SEQUENCE OF OBSERVATIONS IN A DOG BOTH OF WHOSE HIND LEGS WERE SNUGLY BOUND WITH PLASTER BANDAGES BEFORE STARTING THE EXPERIMENT. THE TIME OF EACH PERIOD OF URINE COLLECTION IS INDICATED IN MINUTES. THE ASTERISK OPPOSITE THE ARTERIAL PRESSURE (PERIOD 9) INDICATES THAT IT DROPPED MOMENTARILY TO 156 MM. HG. AS EACH TOURNIQUET WAS RELEASED

Urine Collection Period	Plasma Clearances		Filtration Fraction	Urine Vol. Cc. Per Min.	Hematocrit Index Per Cent	Arterial Pressure Mm. Hg.	Time Min.	Remarks
	Diodrast Cc. Per Min.	Inulin Cc. Per Min.						
1–3	248	81	0.32	0.2	56	158	30	Control
4	258	77.4	0.30	0.15	59	148	46.75	(2) Tourniquets applied
5	263	75.6	0.28	0.12	58	158	46.0	
6	236	69	0.29	0.11	56	158–166	48.25	
7	231	71.1	0.31	0.18	57	168	47.25	
8	234	72	0.30	0.3	57	166	17.0	
9	213	73.4	0.34	0.15	57	164*	12.25	(3) Tourniquets released
10	246	82.5	0.34	0.2		166	20	
11	223	73	0.33	0.1	57	166	24.5	

DISCUSSION

The death of many animals in this series indicates that the observations reported were in fact made during "the onset of shock." This view is supported by the clinical and anatomic evidences of death in shock which appeared in 15 normal and 12 splenectomized dogs subjected to a similar four-hour period of tourniquet application (Taylor and Page, 1943). We are, therefore, lead to believe (Chart 1) that the onset of shock due to tourniquet application and release is associated with severe depression of renal function.

The oliguria may result, in a measure, from secretion of hypophyseal antidiuretic hormone as the result of painful stimulation (Rydin and Verney, 1938) for it had its onset often before large changes in the renal clearances of diodrast and inulin. As to the latter, the observations in the dogs with subcutaneously explanted kidneys establish that, as in normal dogs (White and Heinbecker, 1940, and Corcoran, Smith and Page, 1941) plasma diodrast clearance during tourniquet application may be considered as measuring the rate of renal plasma flow to functioning excretory tissue (Smith, Goldring and Chasis, 1938), while plasma inulin clearance is accepted as the measure of the rate at which glomerular filtrate is formed from renal plasma (Smith, 1939). By this construction, the depression of renal function which appears during the onset of shock is essentially due to reduction of renal blood flow. It, thus, becomes our purpose to determine the nature and origin of this renal ischemia.

Renal ischemia during shock might be due to hypotension alone or to some redistribution of blood in response to decreased blood volume. Actually, a comparison of the levels of renal perfusion and arterial pressure 45 minutes after tourniquet application with these values in hypotension due to a large hemorrhage (Corcoran and Page, 1943) indicates that the reduction of blood flow is not simply the result of lowered arterial pressure and decreased blood volume. This impression is confirmed by the experiments summarized in Chart 2, where transfusion of large amounts of blood caused

only a modest restoration of renal plasma flow towards the normal. The renal ischemia of early shock is, therefore, not the result of hypotension, and, it follows, that it must arise in increased renal resistance to the flow of blood. That renal resistance rises is shown graphically in Chart 4, where are plotted concurrent changes in total renal blood flow and renal arteriolar

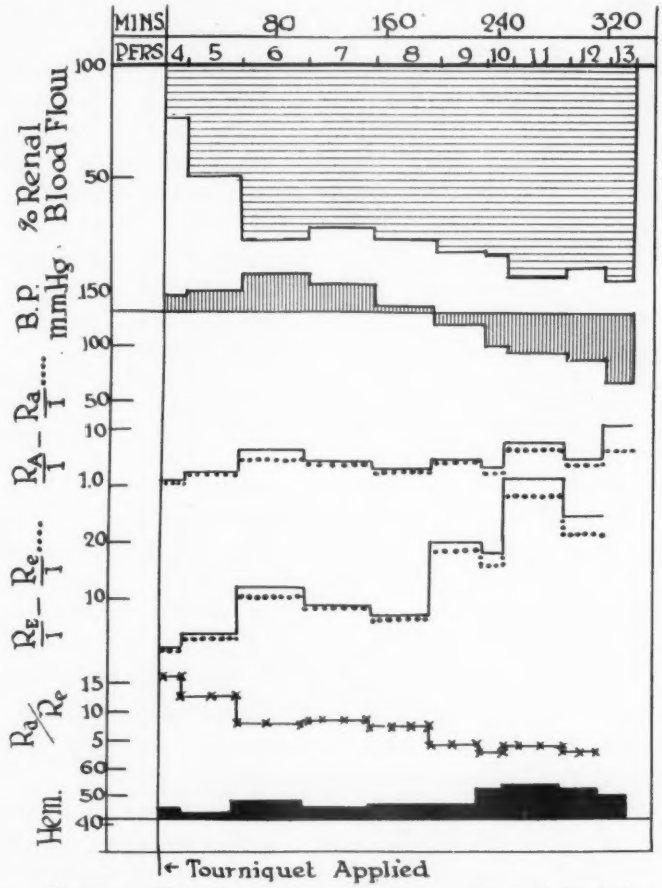

CHART 4.—Effect of tourniquet application on total renal blood flow, blood pressure (B. P., mm. Hg.) calculated renal resistance and hematocrit index in a normal dog with subcutaneously explanted kidney. The values of resistance (R) are shown as ratios of the control level which is taken as equal to 1; R_A, total afferent arteriolar resistance; R_a, the same corrected for changes of blood viscosity; R_E, total efferent arteriolar resistance; R_e, the same corrected for viscosity. The ratio R_a/R_e expresses the relative changes of arteriolar resistance proximal and distal to the glomeruli. Hem. = hematocrit index.

resistance, the latter calculated by the method of Lamport (1943), and considered in relation to the control level.

It might be supposed that a significant factor in this resistance to blood flow might lie in the viscous resistance due to erythremia (increased hematocrit index). That this is not a large element in the renal ischemia is shown in those experiments in which erythremia was abolished by splenectomy, at least until the tourniquets were released (Chart 3). In passing,

it should be noted that this effect of splenectomy extends and confirms the observations reported by Taylor and Page (1943). Lamport (1943) has proposed a nomogram by which the relative influence of viscous resistance due to changes in hematocrit index and plasma protein content may be estimated, and he suggests that this factor be applied to calculated renal arteriolar resistance, with the advantage that the values of apparent arteriolar resistance thus determined represent only the changes due to alterations in the blood vessels. We applied this correction to the values obtained in two experiments (Nos. 3 and 6) and, as shown in Chart 4 (from Experiment 3), found that erythremia accounted for only a small fraction of the resistance which developed in the renal circulation. We must, then, conclude that the increased renal resistance to blood flow during the onset of shock is the result of actual vasoconstriction. The calculations made both from Experiments 3 and 6 indicate that this resistance develops predominantly in the glomerular efferent arterioles.

Such a renal vasoconstriction might develop during the onset of shock on the one hand by operation of nervous influences, as from pain at the site of tourniquet application and in swelling limbs, or, reflexly, from hypovolemia, or, on the other hand, it might be due to the activity of humorally circulating vasoconstrictor substances.

That the renal nerves are not the predominant influences in the increased renal vascular resistance is shown by experiments in dogs subjected to renal denervation, both splenectomized (Chart 3) and nonsplenectomized (Experiment 2, above). However, it is noteworthy that renal plasma flow (from diodrast clearance) did not decrease in these to the very low levels of 25 per cent of the control which was observed in normal dogs (Charts 1 and 2). The fact that blood was transfused during the experiments shown in Chart 3 does not alone explain the partial maintenance of renal perfusion during tourniquet application, for the infusion was very slow. Further, no infusion was given at this phase of Experiment 11, and here, the reduction of blood flow prior to release of the tourniquets was even less marked than in the group to which blood was given. Neurogenic renal vasoconstriction, possibly the result of pain, is, as are hypotension and hypovolemia, a factor in the genesis of renal ischemia during the onset of shock. But it is not the important factor, for there remains a reduction of renal plasma flow to about 50 per cent of the control levels when the combined influences of renal nerves, of erythremia and, in large measure, of hypotension and hypovolemia are excluded respectively by renal denervation, splenectomy and blood transfusion (Chart 3).

There remains only the probability that most of the renal ischemia, with which we are here concerned, is due to the release into the blood of a humorally circulating vasoconstrictor material. Such a "peripheral vasoconstrictor substance" appears in plasma during procedures which cause shock (Page, 1943), and it was shown to develop in plasma during six of seven experi-

ments of this report. Interestingly, the only dog in whose plasma it did not develop, *viz.*, the one suffering from renal hypertension, also showed only a slight depression of renal plasma flow in most periods and, because of the increase in hematocrit, an actual rise of renal blood flow in some. Similarly, although no determinations of vasoconstrictor substance were made in Experiment 13, the absence of renal vasoconstriction in the animal whose limbs had been wrapped in plaster bandages before applying the tourniquets suggests that formation of the vasoconstrictor material had been inhibited by this procedure. Katz, Shleser, Asher and Perlow (1942) have observed a preventative action of limb encasements on shock due to the analogous procedure of venous occlusion, although they attributed this effect entirely to the prevention of loss of blood volume, while our experiment with the limb encasements suggests that failure of formation of vasoconstrictor substance may also be concerned. Indeed, circulatory depression due to release of this substance should, it seems to us, be reckoned among the harmful effects of tourniquets which, of course, include pain and sudden loss of blood volume (Wilson and Roome, 1936). In this connection, the observations of Blalock (1943) on the presence of a toxic substance in the thoracic lymph of dogs with injured hind legs might be cited, although no evidence is available to establish a relationship between Blalock's "toxic products" and the "peripheral vasoconstrictor substance" of Page. Duncan and Blalock (1943) have recently confirmed the widely held clinical view that release of a tourniquet long applied to an injured extremity is dangerous and often lethal. The systemic activity of "vasoconstrictor substance" probably enters into this effect.

The mechanism of the decrease in diodrast extraction ratio during circulatory depression after tourniquet release is not clear. We have observed a similar change during the renal circulatory adjustments which follow hypotension due to bleeding (Corcoran and Page, 1943) and the cause of the abnormality seemed to lie in a change in the equilibrium between plasma and renal interstitial fluid. In the present experiments, other factors, such as arteriovenous shunting or renal epithelial injury might also be adduced. Whatever its nature, this depression of diodrast extraction ratio has the effect that diodrast clearance no longer measures renal plasma flow as well as it normally does or as it did during the period when the tourniquets were still in place. Thus, interpretation of diodrast clearance as the equivalent of renal plasma flow is unwarranted after tourniquet release or analogous injury, as, also, after severe and repeated hemorrhage. Further, the resultant decrease of diodrast clearance in ratio to inulin clearance also alters the significance of filtration fraction, which cannot remain as an expression of relative levels of intraglomerular pressure or the equivalent of inulin extraction ratio. An increase of filtration fraction after severe injury is not always evidence of increased intraglomerular pressure, although such may develop. When intraglomerular pressure increases after injury, it may be because of efferent arteriolar constriction, as in Experiment 3 (Chart 4), or,

when it fails to appear, it may be because the efferent constriction was accompanied by systemic hypotension (as in Experiment 6).

A few deductions may be made from the clinical point of view: First; and in accord with clinical impressions, we note that the renal resistance which develops during the tissue of tourniquet application is more intense than the resistance which slowly appears after severe and repeated bleeding (Corcoran and Page, 1943) where the tissue injury is presumably milder and more diffuse. Second, fear of interfering with blood flow as the result of increased viscous resistance due to erythremia is probably unwarranted under most circumstances, so that transfusion of blood should not be delayed because plasma, otherwise desired, is temporarily unavailable. Third, with reference to "traumatic anuria," *i.e.*, the persistent and often recoverable loss of renal function which may follow crushing injuries or circulatory obstruction (for review see Editorial, Brit. Med. Jour., 1942) the complete recovery seen in Experiment 1 (and in other similar experiments shortly to be published) indicates that tourniquet application alone does not satisfactorily reproduce this type of renal injury, nor cause lasting depression of excretory function. Indeed, sections of the kidneys of two of our dogs after death, which had ensued from four-hour application of tourniquets, did not have the appearance of early "traumatic anuria" described by Bywaters and Dible (1942). However, the severe hemodynamic changes which do appear in the kidney during and after tourniquet release are sufficient explanation for subsequent transient signs of renal irritation without excretory failure, such as were observed after limb crushing by Duncan and Blalock (1942). Our failure to reproduce the syndrome of traumatic anuria by a procedure which depends upon massive swelling of limbs suggests also that the explanation of the syndrome as the simple result of excessive fluid loss is unsatisfactory. Finally, pending a full explanation, consideration should be given the view that traumatic anuria depends upon myoglobin aggregating in and plugging or poisoning renal tubules (Bywaters and Beall, 1941), and, with this view in mind, certain points arising from our experiments may be recalled. Thus, (a) the depressed renal blood flow and filtration rate of severe injury would largely tend to prevent excretion of myoglobin from plasma and its consequent deposition in tubules until renal excretory function had been improved by treatment of shock. Therefore, (b) measures of urinary alkalinization and diuresis, such as those proposed by Bushby, Hart, Kerwick and Whitby (1940), might well be adopted before transfusion of blood or plasma in patients with crushing injuries. However, (c) since renal function is depressed during the onset of shock, so that myoglobin may tend particularly to injure tubules at this time, measures for the relief of shock should themselves tend to prevent renal failure.

SUMMARY

Onset of shock due to the four-hour application of partially occluding hind limb tourniquets to anesthetized dogs causes a marked depression of

renal function, which is the result of reduction in renal blood flow. The factors which may enter into this decrease of renal blood flow are (1) decreased arterial pressure; and (2) increased renal resistance to the flow of blood. Hypotension, however, is only a minor and inconstant element; increased renal resistance is much more important. Among the causes of increased renal resistance, blood viscosity due to a rise of hematocrit index is not significant, for splenectomy, which prevents the increase of hematocrit, does not interfere with the reduction of renal blood flow. Although renal vasoconstriction of nervous origin is a greater factor than viscous resistance, it, too, accounts for only a small proportion of the renal ischemia which follows tourniquet application and release, as is shown by renal denervation. The decrease in renal blood flow which occurs while limb tourniquets are in place when these factors are excluded, *i.e.*, in dogs previously subjected to renal denervation and splenectomy, and in which arterial pressure and blood volume are maintained by blood transfusion during the experiment, seems to be due to some humorally circulating vasoconstrictor substance. Such a material was demonstrable in the plasma of several animals in which its presence was associated with increased renal resistance, predominantly at the glomerular efferent arterioles. With injury, as after the release of tourniquets, diodrast renal extraction ratio may be depressed, so that normal interpretations cannot be given to changes in plasma diodrast clearance and filtration fraction. The renal vasoconstriction associated with the onset of shock serves to explain transient signs of renal irritation which may follow injuries. Although it may play a part in the genesis of "traumatic anuria" ("crush syndrome") it alone does not reproduce this state.

CONCLUSIONS

1. The depression of renal function during the onset of shock due to partially occluding tourniquets is due to a decrease of renal blood flow which is only in a minor and inconstant measure the result of decreased arterial pressure.

2. This decrease of renal blood flow is due almost wholly to increased renal vascular resistance, into which increased blood viscosity enters only in small degree, the increased resistance being rather due to vasoconstriction, predominantly affecting the glomerular efferent arterioles.

3. Although nervous stimulation, presumably as the result of pain, causes a small measure of this vasoconstriction, much the larger fraction is independent of the renal nerves and, by exclusion, of humoral origin.

4. This humorally-arising renal vasoconstriction is associated with the appearance in plasma of a vasoconstrictor substance to whose activity it is therefore attributed.

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PRIMARY OSTEOGENIC SARCOMA OF THE BLADDER

COMPLETE REVIEW OF SARCOMATA OF THE BLADDER

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ALTHOUGH PRIMARY SARCOMA OF THE BLADDER is an infrequently encountered tumor, we have been able to collect 151 cases from the literature up to 1943. Many histologic types have been reported, but in terms of modern histogenetic classifications, these would be reduced to angiosarcoma, fibrosarcoma and fibromyxosarcoma, malignant lymphoma, leiomyosarcoma, neurogenic sarcoma, rhabdomyosarcoma, chondrosarcoma and osteogenic sarcoma. Undoubtedly, some of the more undifferentiated tumors reported as round cell and spindle cell sarcomata, *etc.*, represent anaplastic carcinomata, or would be more properly classified with the fibrosarcomata. Of the various types, the bone-producing tumors are the rarest and most peculiar from a histogenetic point of view. Eight cases of primary malignant bladder tumors producing bone or cartilage have been collected from the literature (Table I), and it is with this group of tumors that this paper is primarily concerned.

In 1856, Ordonez[1] recorded the first instance of a malignant bladder tumor containing elements of cartilage or bone. His case, occurring in an "old man," is reported as a "chondroma" but is described as "an infiltrating tumor of the bladder composed of a fibrous tissue matrix, containing large numbers of cartilage cells." The bladder was filled with a transparent yellowish-brown gelatinous substance. Further clinical or pathologic details are not given in his report, which deals chiefly with the histologic structure, but the tumor would probably be more accurately classified as a chondrosarcoma.

The second case was reported by Shattock[2] in 1887, who reported a tumor in a 55-year-old male located in the region of the trigone about the right ureter, and productive of hematuria and dysuria for four years. On surgical excision, the tumor was covered by mucous membrane and was in part papillary in form. Histologically, it is described as being composed of cartilage and of a "sarcoma tissue of a spindle and mixed cell variety." The patient died nine months after the operation, and at autopsy showed a large soft growth, two inches in diameter, encroaching on the bladder from the base. The right ureter passed through the middle of the growth and was dilated. The bladder was diffusely infiltrated by the tumor which at this time was found to be a "round-cell sarcoma" and contained no cartilage. There were also multiple papillomatous growths in the bladder. Shattock records the case as one of "chondrifying sarcoma and multiple papillomata." From the material available, any other classification under current terminology is not warranted.

TABLE I

MALIGNANT OSTEOGENIC TUMORS OF THE BLADDER

Date	Author	Sex	Age	Symptoms	Location	Author's Diagnosis	Modern Diagnosis	Metastases	Course
1856	Ordonez[1]	M	Old	?	?	Chondroma	Chondrosarcoma	None	Died
1887	Shattock[2]	M	55	Hematuria, dysuria—4 yrs.	Trigone over right ureter	Chondrilying sarcoma	Chondrosarcoma	None	Died—9 mos.
1899	Beneke[3]	M	72	Hematuria—weeks	Trigone over left ureter	Osteoid chondro sarcoma	Osteogenic sarcoma	None	Died—8 wks., pyelonephritis
1905	Heisler[4]	?	1½	?	Posterior bladder wall	Fibro-edemato-myo-enchondroma	?	?	?
1908	Fischer[5]	F	62	Hematuria, dysuria, obstruction—5 mos.	Base of bladder on right	Osteoid chondrosarcoma	Osteogenic sarcoma	Local, pleura omentum	Died—days. Cachexia, hydronephrosis
1913	Ried[6]	M	57	Hematuria, dysuria, obstruction—6 mos.	?	Chondromyxosarcoma	Osteogenic sarcoma	Invasion of rectum	Died—4 mos. Cachexia
1929	Wright—Smith[7]	M	47	Hematuria, dysuria, frequency—5 wks.	Superior surface	Teratogenous sarcoma	Osteogenic sarcoma	None	Died—6 days.
1938	Droschl[8]	M	67	Weight loss—1 yr. Frequency—6 wks.	Trigone over right ureter	Osteoid sarcoma	Osteogenic sarcoma	?	Died—1 day, postoperative
1943	Crane & Tremblay	M	69	Hematuria—6 mos. Dysuria—2 mos.	Trigone over left ureter	Osteogenic sarcoma	Osteogenic sarcoma	Local, pelvic abdominal wall, intestinal serosa lung	Died—4½ mos. Cachexia, uremia, pyelonephritis

These first two recorded cases dealt with tumors containing cartilage. Then, in 1899, Beneke[3] reported a case of osteochondrosarcoma, this being the first one described as producing bone. A 72-year-old male with a history of hematuria of a few weeks' duration, at operation showed a pedunculated tumor, the size of a "small apple" originating at the lateral edge of the trigone and covering the mouth of the left ureter. The tumor was excised. Grossly, it was mushroom in shape, hard, and showed trabeculations having the consistency of bone. Histologically, it showed much osteoid tissue and in some areas bone with osteoclasts. Other portions were very cellular, most of the cells being spindle-shaped. Areas of hyalin cartilage shading into zones of active bone formation and bone marrow were also present. The patient died eight weeks after operation of pyelonephritis. At autopsy, there was invasion of the bladder by the tumor which showed the same histologic structures described above. Skeletal muscle fibers were also present. Only local extension metastases occurred. There is no question that this tumor belongs in the group of osteogenic sarcomata.

In 1905, Heisler[4] reported a "fibro-edemato-myoenchondroma" occurring on the posterior bladder wall of a one and one-half-year-old infant. This case was cited by Fischer, but we have been unable to find the original article.

Fischer,[5] in 1908, reported the first case of an osteogenic sarcoma with distal metastases. This was a 62-year-old female, with a five-months' history of hematuria, dysuria, urinary obstruction, and emaciation, who died following a cystotomy. At autopsy, a tumor 7.0 x 5.0 x 5.5 cm. was found at the base of the bladder on the right side. Grossly, it was encrusted, hard and white. Microscopically, it contained bone, cartilage and fibrous tissue elements. Metastases were present in the pleura, omentum and about the right ureter, and all of these presented the same histology as the original tumor. There were also marked bilateral hydroureters and hydronephrosis and a bronchopneumonia. Fischer reported this as an osteochondrosarcoma.

Ried,[6] in 1913, published a case of chondromyxosarcoma in a 57-year-old male with a six-months' history of hematuria, dysuria and increasing urinary obstruction. At operation, a hard tumor completely filling the bladder was found. Microscopically, it showed a varied cellular structure interpreted as sarcoma with areas of osteoid material, osteoclastic giant cells and areas resembling osteitis fibrosa cystica. At autopsy, four months later, the tumor had diffusely infiltrated the bladder wall and rectum, but there were no other metastases. This tumor, we believe, can also be classified as an osteogenic sarcoma.

In 1929, Wright-Smith[7] encountered at autopsy a bladder tumor in a male, age 47, with a history of hematuria, dysuria, nocturia and frequency of five weeks' duration. The tumor projected into the bladder from the superior surface. Histologically, it was composed of spindle-shaped cells and many areas of embryonic cartilage and showed patchy calcification and

many large giant cells (? osteoclasts). The case is reported as a teratogenous sarcoma but may again be classified as an osteogenic sarcoma.

The last case was recorded, in 1938, by Droschl[8] as an osteoid sarcoma occurring in a 67-year-old male with a history of loss of weight for one year, and frequency and urgency for six weeks. At operation, a pedunculated tumor, the size of an apple, was found arising from the region of the trigone and overlying the right ureter. Microscopically, it was composed of closely packed spindle cells ramifying between which were bands of osteoid material. Multinucleated giant cells (? osteoclasts) were numerous. Many blood vessels showed invasion by the tumor cells. The patient died one day after operation and an autopsy, limited to the genito-urinary tract, showed no local metastases.

To these cases we are adding another which is the first to have been studied chemically and histochemically as well as histologically.

Case Report.—J. W. B., a 69-year-old married white fireman, came to the hospital, with a chief complaint of hematuria. His past history was entirely negative save for: (1) Typhoid fever 25 years ago; and (2) fracture of right lower extremity five years ago. The family history, systemic review and personal history were non-contributory.

Present Illness: Six months before his first admission on January 13, 1943, he noted the onset of gross hematuria. He passed blood throughout micturition. He consulted his physician who prescribed pyridium. Following administration of this drug, the gross hematuria disappeared, and the patient was symptom-free during the next three months. However, during the two months before being admitted to the hospital, he noted hematuria on five separate occasions. The hematuria was now associated with marked dysuria especially toward the end of micturition and on the last two occasions, he passed small blood clots.

Physical Examination: The patient was a well-developed and well-nourished white male. Temperature 99, pulse 84, respirations 20, blood pressure 170/80. The positive physical findings included: Edentulous upper and lower jaws. Lungs—clear to percussion and auscultation save for atelectatic râles at both bases posteriorly; Heart—no abnormalities except for distant heart sounds. Abdomen—entirely negative. Bladder not distended. Extremities—slight angular deformity just above right angle, at site of previous healed fracture. Rectal—prostate slightly enlarged, especially the right lobe and presents two irregular nodular areas about 0.5 cm. in diameter. There is no impression of fixation of the gland and its consistency though firm is not stony hard. No rectal masses were felt nor was there any blood on the examining finger.

Progress: The patient was catheterized after voiding and two ounces of grossly bloody urine obtained. The next day on cystoscopy, some difficulty was encountered in passing the instrument through the bladder neck but after some manipulation toward the right, it entered the cavity of the bladder. A large, irregular greyish-yellow mass was seen to the left of the midline and lying over the bladder floor. There was no visible viable tissue and, on motion of the cystoscope against this mass, a grating sensation was felt. The diagnosis of a large vesicle calculus was made, and on the second hospital day, a suprapubic cystotomy was performed. On opening the bladder, an oval, lobular, firm tumor, 10 cm. in diameter, was encountered. The tumor was attached to a stalk 5 cm. in diameter at its base and having its origin partially covering the left ureteral orifice. The surface of this tumor was covered with what appeared grossly to be phosphatic deposits. The tumor was removed by dissection and the base thoroughly cauterized. Thorough exploration of the bladder revealed no other abnormalities

save for an hypertrophied prostate. The patient's postoperative course was not remarkable. On the tenth postoperative day, a second-stage prostatectomy was performed. The gland proved to be markedly adherent to the capsule and was enucleated with difficulty. His postoperative course following the second operation was also uncomplicated.

The tumor which had been removed from the bladder was reported by the pathologist to be an osteogenic sarcoma, and the prostatic tissue which was removed

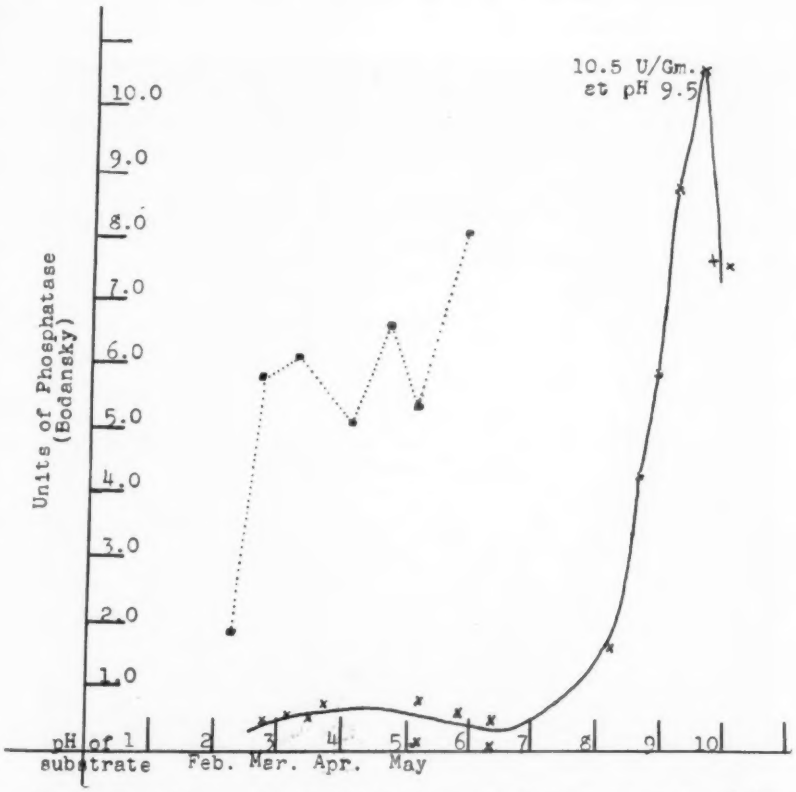


FIG. 1.—The solid line shows the phosphatase content of the tumor per gm. of tissue with a substrate of various *p*H levels. Determinations on the original tumor and the metastases are identical.
..... The dotted line shows the serum alkaline phosphatase during life. For this curve each gradation of the abscissa equals one month.

revealed chronic prostatitis, benign adenomatous hyperplasia and two small microscopic areas interpreted as adenocarcinoma. Radiographs of the chest, shoulder and pelvic girdles, and lumbar spine failed to reveal any evidences of metastases. An intravenous urogram showed that the kidneys were slow in excreting the dye. No definite renal pelvis could be outlined on the left side, but the right renal pelvis appeared normal. Following this, repeated blood chemistry studies were made. The serum calcium ranged between 11.4 and 13.0, and the serum phosphorous between 2.9 and 3.3. The total serum proteins were 5.9, albumin 2.7 and globulin 3.2. The urea nitrogen averaged 20 mg. The urea clearance test revealed a kidney function of 19.8%. The Mosenthal test showed a fixed specific gravity ranging from 1.013 to 1.016. The blood Wassermann, Kahn, and Hinton tests were negative. A urine culture revealed a heavy growth of *B. subtilis*. The blood count which on admission had shown 10.4 Gm. (70%) hemoglobin

and 4,100,000 red blood cells had dropped to 8.0 Gm. (53%) hemoglobin, with 4,100,000 red blood cells at the end of his fourth week in the hospital. The serum alkaline phosphatase, which had ranged between 1.3 and 1.7 immediately after removal of the tumor, rose to 5.9 (Fig. 1) on the 34th day after the first operation. A cystogram (Fig. 2) done at this time showed a filling defect in the left side of the bladder wall. Cystoscopy revealed a well-funnelized bladder neck. The right ureteral orifice appeared normal. The left ureteral orifice could not be seen. On the left lateral wall posteriorly, there was a rounded, elevated smooth mass 2.5 cm. in diameter and 1.0 cm. in height and adjacent to this another mass 1.5 cm. x 0.5 cm. both having the appearance of

FIG. 2.—Cystogram showing abnormal shape of bladder and filling defect on the left.

new growths. The alkaline phosphatase continued to range between 5.5 and 5.9 up to the time of the patient's discharge from the hospital on February 25, 1943, on his 43rd hospital day. His general condition at the time of discharge was good, and he was symptom-free.

One week after leaving the hospital, he developed a painful swelling of his right testis. At the same time, he began to have urinary frequency, dysuria, urgency and incontinence of urine of a mild degree. On March 8, 1943, he entered the hospital for the second time. Physical examination at this time revealed the following additional findings: A well-healed midline suprapubic scar, a swollen, tender right testicle. Roentgenograms of the chest, shoulder and pelvic girdles, and lumbar spine were repeated, and still failed to show any evidence of metastases. A radiograph of the skull, however, showed an area of rarefaction 4.5 cm. in diameter in the right

parietotemporal region and several small punched-out areas scattered throughout the skull. A cystogram of the bladder revealed a filling defect involving nearly all of the left hemisphere of the bladder. Cystoscopy showed an irregular infiltrating tumor which entirely filled the left half of the bladder. Several pieces of tissue were taken with a biopsy forceps and again showed an osteogenic sarcoma. The serum alkaline phosphatase at the time of his second admission was 6.0.

On March 29, 1943 a subcutaneous nodule 1.5 cm. in diameter, which had first made its appearance one week before and had been increasing rapidly in size, was biopsied, and the specimen reported to be osteogenic sarcoma. The patient continued progressively downhill. One month before his death, the suprapubic scar broke down and he began to drain urine through the opening. Two other subcutaneous nodules made their appearance, one above and one below this opening. His urea nitrogen which had been 35.0 and creatinine 3.2 at the time of his second admission gradually rose to 80.0 and 5.2, respectively. He became progressively more drowsy and finally comatose two days before his death. His alkaline phosphatase was 8.0 at this time. The acid phosphatase ranged from 0.5 to 0.6 on repeated determinations. He had a generalized convulsion 12 hours before his death. His respirations became labored and his pulse weak, and he finally died on May 24, 1943, four and one-half months after his operation, and ten and one-half months after onset of symptoms.

PATHOLOGIC STUDIES

The original tumor (S 43–48) was removed in pieces varying from 0.6 to 6 cm. in diameter and weighing 104 Gm. Externally, the fragments were rough and irregular and had a brown, encrusted surface. The cut surfaces were white, hard, and gritty. Microscopically (Fig. 4), multiple sections showed irregular anastamosing bands of a dense, acellular, eosinophilic material between which were single or small groups of polyhedral to spindle-shaped tumor cells with large, central, oval to round, vesicular but hyperchromatic nuclei. At many points, these cells were arranged along the margins of the intercellular substance like osteoblasts. Large osteoclastic giant cells were present, and there were also groups of cartilage cells. Mitoses were numerous and the tumor could be seen invading capillaries. A crystal violet stain for amyloid was negative. Mallory's aniline blue and phosphotungstic acid-hematoxylin stains were negative for intracellular fibrils, and Weigert's stain for elastic tissue showed none within the tumor. Subsequent biopsies of the bladder tumor (S 43–209) and incisional metastases (S 43–275) occurring during life showed an identical histologic structure and were similarly interpreted. *Pathologic Diagnois:* Osteogenic sarcoma.

The prostate (S 43–84) weighed 10 Gm. and showed a typical benign adenomatous hyperplasia, chronic prostatitis, and two small foci of irregular arrangement of the glands interpreted as microscopic foci of adenocarcinoma.

The autopsy (A 43–1591) was performed about 30 minutes after death; only the positive findings are given. Inspection: The body was that of an emaciated, adult, white male. The abdomen presented two nodules located in the midline just above the symphysis pubis. Each measured about 5.5 cm. in diameter, was firm, and covered by a flattened, tense, bluish skin. Between the two nodules was an opening 0.3 cm. in diameter which communicated with the bladder. The right lower extremity presented a deformity of the tibia 3 cm. above the internal malleolus which was a hard, bony thickening measuring 4 x 2 cm. at the site of an old fracture. Only the inguinal lymph nodes were enlarged and these were all less than 1 cm. in diameter. Peritoneal Cavity: The pelvis contained a large mass, about 18 x 10 cm., continuous with the bladder and the skin nodules. There were no adhesions between the mass and any abdominal organs, and it did not invade the rectum. Thorax: About 10 cc. of fluid was present in each pleural cavity, and the pleural surfaces of each lung contained multiple, hard, white tumor nodules, 0.5 to 2 cm. in diameter. Heart: Negative,

Aorta: Moderate atherosclerosis of the abdominal portion. Lungs: The left weighed 325 Gm.; the right 450 Gm. Each showed multiple pleural and parenchymal, circumscribed, hard, white tumor nodules 0.5 to 2. cm. in diameter. Spleen: Negative. G. I. Tract: There was a Meckel's diverticulum, 5 x 3 cm., of the ileum, and a few small (0.2 cm.), white nodules in the mesentery at the edge of the small bowel. Pancreas and Liver: Negative. Kidneys: The left weighed 80 Gm.; the right 150 Gm. Each showed a marked dilatation of the ureter and pelvis and contained a yellow, purulent material. The surfaces were irregularly granular and showed flat depressed scars and small, yellow abscess nodules 0.1 to 0.2 cm. in diameter. On the cut surface the pyramids were indistinct. Adrenals: Negative. Bladder (Fig. 3): Measured about 12 cm. in diameter and was entirely filled by a grayish-green, cauliflower-like growth growing from a broad base covering most of the posterior and superior bladder

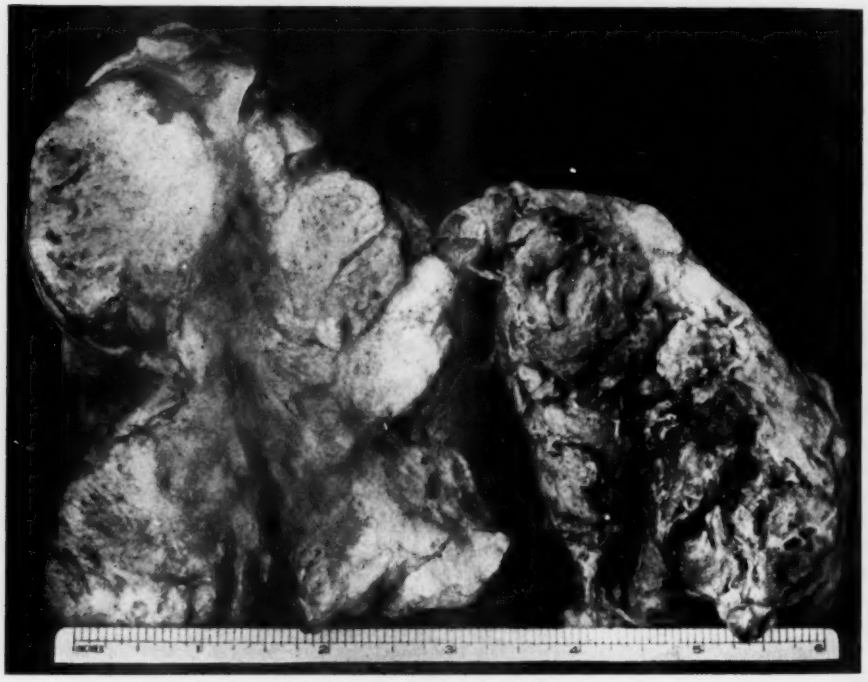


FIG. 3.—Gross specimen hemisected longitudinally. The bladder, with the fungating mass, lies to the right. To the left is the anterior bladder wall and the huge mass of tumor invading the abdominal wall. Skin and pubic hairs may be seen at the left margin.

walls. On section, the mass was hard, gritty, firm and white. The posterior bladder wall was thickened, measuring 3 cm., and was also firm, white, and gritty, being diffusely infiltrated by tumor tissue. The anterior bladder wall was 0.4 cm. thick, gray-green and necrotic. The ureters opened directly into the tumor mass and were markedly constricted by it. Genital Organs: Negative save for surgical absence of the prostate. Bone Marrow: Negative. Lymph Nodes: Negative; none showed any tumor metastases. Head: The skull showed no evidence of metastatic tumor and the brain was negative.

Microscopic: Tumor: Sections of the bladder tumor, bladder wall infiltrated by tumor, skin nodules, mesenteric and pulmonary metastases all showed a similar histologic picture identical with that described in the original surgical specimen (S 43–48). The tumor cells resembled osteoblasts and there was much osteoid material, osteoclastic giant cells and cartilage (Fig. 4). Mitoses were numerous. Stains for alkaline phosphatase (Fig. 5) showed large amounts in the cells and intercellular tissue of the more

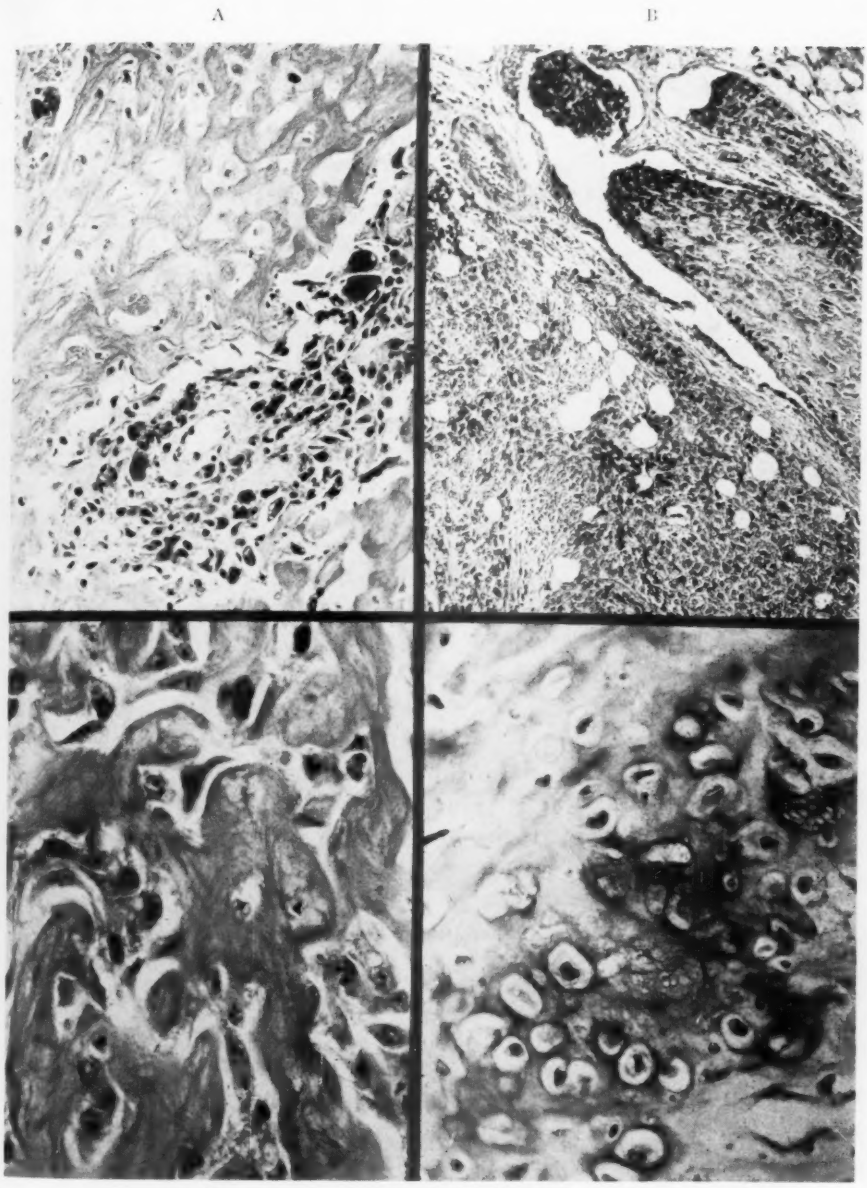


FIG. 4.—(A) Adult bony portion of primary tumor showing osteoid material, osteoblasts and osteoclastic giant cells. Phloxine-methylene blue. (×130)

(B) More cellular portion of a local extension of the primary tumor showing blood vessel invasion. Phloxine-methylene blue. (×110)

(C) Osteoid zone of primary tumor showing osteoblasts and intercellular substance. Phloxine-methylene blue. (×335)

(D) Cartilaginous zone of primary tumor showing large cartilage cells. Phloxine-methylene blue. (×335)

cellular portions and none in the osteoid material. Stains for acid phosphatase were negative. Kidneys: Showed interstitial scarring and lymphocytic infiltration, with compression of the tubules, many of which contained colloid-like casts. Some contained masses of bacteria and neutrocytes. Meckel's Diverticulum: Contained gastric mucosa. Tibia and Skull: Negative for tumor tissue.

Chemical Analysis: H. Q. Woodard, Ph.D., of Memorial Hospital, N. Y. C. extracted the tumor and the metastases and determined the phosphatase activity at different p_H levels (Fig. 1). In the acid range less than 6.5 units per Gm. were present but in the alkaline range there was a sharp increase to 10.5 units per Gm. at a p_H of 9.5.

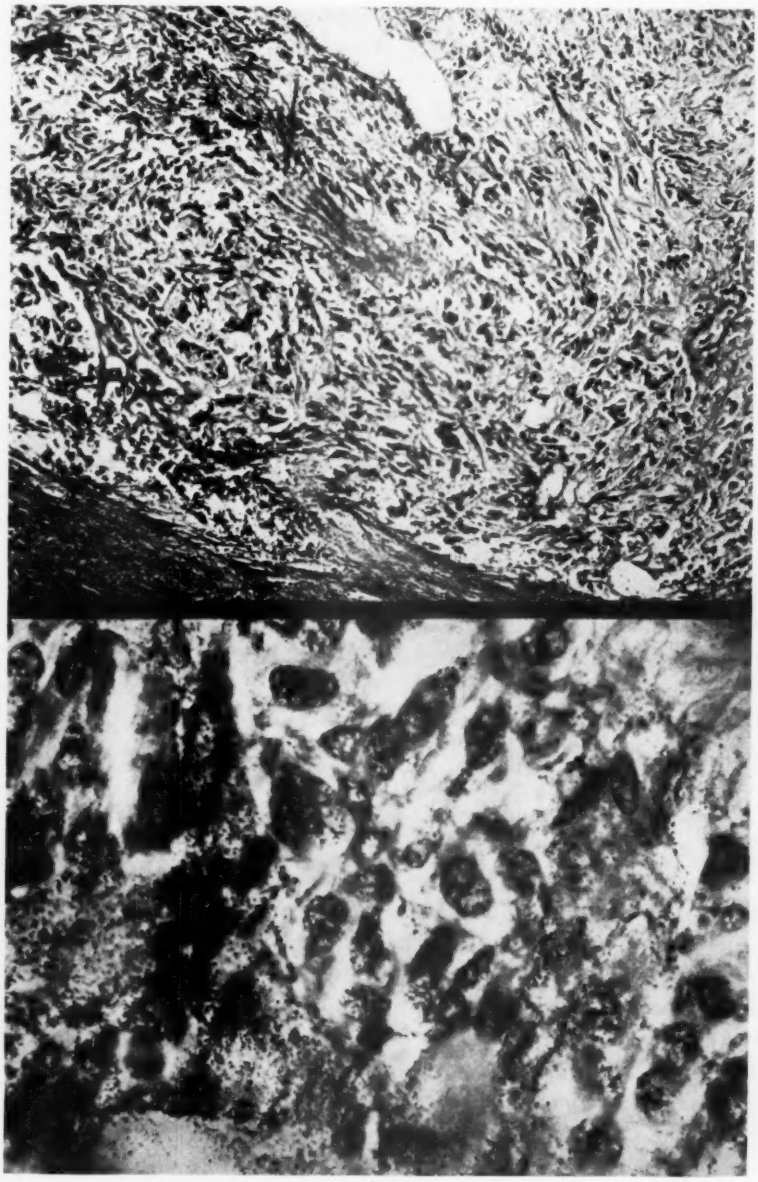
Anatomic Diagnoses: Osteogenic sarcoma of the bladder, with metastases to the abdominal wall, pelvic cavity, lungs and intestinal serosa; chronic cystitis; chronic pyelonephritis; bilateral pyonephrosis and pyoureter; vesicle sinus; Meckel's diverticulum with heterotopic gastric mucosa; aspermatogenesis of the testes; cysts of the choroid plexus; healed fracture of the right tibia; and moderate aortic atherosclerosis.

Discussion.—Here we have a malignant tumor, which both in the original and in the metastases is producing bone with polyhedral to spindle cells resembling osteoblasts, an osteoid stroma, osteoclastic giant cells and cartilage. From a purely histologic viewpoint it should be classified as an osteogenic sarcoma. This diagnosis is substantiated by the chemical extraction of the tumor showing little or no phosphatase activity in the acid range and a sharp rise in phosphatase activity in the alkaline range to a maximum of 10.5 units at a p_H of 9.5 (Fig. 1). Such a curve of phosphatase activity has been found by Woodard,[9] and by Woodard and Higinbotham,[10] only in the more cellular (rapidly growing) forms of osteogenic sarcoma. The diagnosis is further supported by the histochemical distribution of alkaline phosphatase occurring both intracellularly and intercellularly, as described by Gomori,[11] and by Kabat and Furth,[12] in osteogenic tissues and tumors. Of final confirmatory value is the progressive rise in serum alkaline phosphatase during life (Fig. 1). It is of interest that following the first excision of the tumor when proliferating osteoblasts were minimal, the serum alkaline phosphatase was low. Then, as the tumor recurred and increased in size, the phosphatase values of the serum rose progressively, practically paralleling the recurrence of the tumor tissue. This is in accord with the observations of Franseen[13] on primary bone tumors.

What is the origin of such tumors? Two possibilities have been suggested by previous writers:[3, 6] First, that they represent a metaplasia of bladder mucosa; and, secondly, that they are derived from embryologic rests of the wolffian body, from which the trigone of the bladder develops. Sarcoma of the bladder is a rare tumor in itself, and of the 151 cases collected from the literature only nine, or six per cent, may be called osteogenic. Considering the much greater frequency of carcinomata, the question arises as to whether these bone-producing tumors are not examples of extreme metaplasia occurring in epithelial tumors. That they do produce bone must be admitted, but if the cells are epithelial, one would then have to accept the term "osteogenic carcinoma." Several items serve to add interest to the

conjecture of the possible epithelial origin of the tumors. Greenstein[14] has shown that intestinal mucosa and the kidney of mice and the Jensen sarcoma and transplantable hepatoma of rats contain large amounts of alkaline

A



B

FIG. 5.—(A) Stain for alkaline phosphatase on the original tumor. The phosphatase (precipitated silver) has rendered the cells into dark black masses. (×80)
(B) Same as (A) but higher magnification. (×700)

phosphatase. Woodard[15] has shown that the liver cancer produced in rats by the feeding of p-dimethylaminoazobenzene contains large amounts of

alkaline B-glyerophosphatase. White, Dalton and Edwards[16] have noted that these induced hepatomata frequently calcify. However, in none of these instances is there a phosphatase content as high as that reported in osteogenic sarcoma. Kabat and Furth[12] have described large amounts of phosphatase occurring in the epithelium of the renal pelvis and the bladder mucosa of mouse embryos, and this lessens the diagnostic value of the histochemical demonstration of phosphatase in regard to settling the question of the nature of the proliferating cells in these osteogenic tumors. Since phosphatase plays an important rôle in bone formation, the possible derivation of such tumors from these phosphatase-rich cells must be considered. However, this would entail the admission of the development of bone and cartilage from epithelial cells, other evidence for which is lacking both in normal tissues and tumors of the genito-urinary system in which the occurrence of bone is infrequent. Chemical and histochemical determinations on epithelial tumors of the bladder will serve to clarify the subject.

It is more plausible to assume that the phosphatase content of the epithelial cells may influence subsequent development of tumors derived originally from mesodermal elements. Neuhof[17] has shown that transplants of fat and fascia to the bladder of dogs ossify. This, he interpreted, as metaplasia due to the stimulation of calcium salts derived from the urine. This along with the infrequency of ossification of the epithelial tumors of the bladder suggests that the ossification is due to the stimulation of mesodermal elements. Huggins[17a] has shown that bladder, ureter and renal pelvis epithelium stimulate the formation of bone about transplants made into certain parietal fascias (rectus sheath, fascia lata and subcutaneous tissue) and in muscle and synovial membrane in the dog. This effect he attributed to the high calcium and phosphorous content in cysts developing at the site of the epithelial transplants and a greater permeability of the newly formed epithelium lining the cysts. Urinary epithelial transplants into kidney, liver, spleen and the connective tissue wall of the bladder did not ossify and Huggins differentiated, on physiologic grounds, the fibrocytes developing around transplants in these locations from those of fascia where ossification occurred. This latter finding lends further support to the concept that osteogenic tumors occurring in the bladder of man develop from embryologic rests stimulated by both the phosphatase content of the urinary epithelium and its ability to cause high concentrations of calcium and phosphorous locally. The frequent location of sarcomata of the bladder in and about the trigone (Table II) has been interpreted as evidence of their origin from remnants of the wolffian body from which the trigone is developed. While only fifty per cent of the cases reported clearly indicate an origin in the region of the trigone fully half of the remainder also involved this region. Numerous dermoid cysts containing skin, hair, teeth, bone, cartilage, *etc.*, have also been reported in this location.[18, 19] The combined evidence would indicate that mesodermal elements derived from the wolffian body may persist in the region of the trigone and give rise to benign or malignant tumors of varied

TABLE II

SHOWING THE AGE AND SEX DISTRIBUTION OF REPORTED CASES AND THE SYMPTOMS, LOCATION OF TUMORS, AND THE HISTOLOGIC TYPES OCCURRING AT VARIOUS DECADES*

Age in Decades		1–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Not Given	Totals	
Cases	M	19	6	6	8	12	22	11	9	1	9	93	
	F	11	3	3	7	6	11	4	2	1		48	151
Symptoms:													
Hematuria		11	6	4	10	13	20	10	8	0	2	84	
Dysuria		9	3	0	5	9	12	10	4	0	1	53	
Frequency		13	2	0	7	8	9	7	4	1	2	53	
Other (pain, cystitis, mass)		16	4	5	4	5	11	8	4	1	0	58	
Location:													
About trigone and ureters		14	2	6	7	6	12	7	3	1	4	62	
Elsewhere		13	7	2	6	12	9	6	5	1	1	62	
Pathologic diagnosis:													
Myo-or leiomyosarcoma		3	2	0	2	1	4	2	3	0	2	19	
Fibrosarcoma		2	0	1	0	0	4	1	0	1	0	9	
Myxosarcoma		3	1	0	1	0	1	0	0	0	1	7	
Probable leiomyo-or fibrosarcoma													
Round cell		5	0	2	4	4	10	1	1	0	2	29	
Spindle cell		3	2	4	1	4	1	1	2	1	2	21	
Mixed cell		2	1	0	2	2	1	3	1	0	0	12	
Osteogenic sarcoma		1	0	0	0	1	2	3	1	0	1	9	
Malignant lymphoma		1	0	0	2	3	1	1	0	0	0	8	
Rhabdomyosarcoma		5	1	0	0	0	0	2	0	0	0	8	
Sarcoma (? type)		2	0	0	1	3	7	1	2	0	1	17	
Other		3	2	2	2	0	2	0	1	0	0	12	
Distant metastases:													
Lung		2	0	0	0	0	1	3	1	0	0	7	
Liver		0	0	0	1	0	1	1	1	0	1	5	
Other		0	0	0	3	0	0	3	1	0	2	9	

*This table is computed from the cases reported by Alberran,[20] ones added by Wilder,[22] and those collected from the literature since 1905 and outlined in Tables I and III. Reports by Munwes[21] and Cecil[39] give many more cases, but the various series listed by them probably represent much reduplication. Carcinosarcomata have been omitted.

cellular structure later in life. In producing only local extension and hematogenous metastases this particular tumor, and the other cases reported, have behaved as do the sarcomata. The histologic structure of our tumor, the location of the early lesion in the region of the trigone, and the occurrence of a second embryologic abnormality in the Meckel's diverticulum with heterotopic gastric mucosa, all lead us to feel that the probable origin of this tumor is from mesodermal remnants of the wolffian body. This probably applies to the other reported cases of malignant osteogenic tumors of the bladder as well.

The possibility of our tumor representing a sclerosing tumor of fibroblastic (desmoid) or smooth muscle origin is unlikely in the absence of any intracellular fibrils with the various special stains despite the fact that the tissue was fresh and fixed immediately. The absence of elastic tissue also supports this concept.

BLADDER SARCOMA

Age and Sex: In our series, cases occurred in all decades, but with a much higher incidence in the first decade, and a second peak in the fifth

TABLE III

CASES OF PRIMARY SARCOMA OF THE BLADDER REPORTED SINCE 1905

Date	Author	Sex	Age	Symptoms	Location	Diagnosis	Metastases	Course
1905	Wilder[22]	M	48	Hematuria, frequency, dysuria—1 yr.	Trigone on left	Round cell sarcoma	?	Died—6 wks.
		M	53	Hematuria, frequency, dysuria, retention—1 yr.	Above left ureter	Fibrosarcoma	?	Died—7 wks., uremia
		M	62	Hematuria, frequency, dysuria—6 mos.	Left lateral wall	Spindle and round cell sarcoma	?	Excision. Living 2 mos. Failing rapidly
1907	Whiteside[23]	F	57	Hematuria, pain, frequency	?	Spindle cell sarcoma	None	Died—2 mos., hydronephrosis
1908	Sottile[24]	M	6 mos.	Retention	Posterior wall	Sarcoma	?	Died—1 wk.
1909	Sicard and Malègne[25]	F	40	Hematuria, dysuria	Diffuse	Sarcoma	None	Died—8 wks., pyelonephritis
1909	Lecène and Chen[26]	M	82	Hematuria, retention	Posterior and superior wall	Fibrocellular sarcoma	None	Died—8 days postoperative
1914	Bockenheimer[27]	F	40	Hematuria, bladder pain, cachexia	Posterior and right lateral wall	Sarcoma	None	Excision. Cured???
1914	Binney[28]	M	74	Frequency	Posterior and left lateral wall	Leiomyosarcoma	None	Died — 3 days, pyelonephritis, uremia
1915	Harpster[29]	F	55	Hematuria	Trigone over left ureter	Mixed cell sarcoma	?	Died—3 days, postoperative
1917	Mixter[30]	F	3½	Hematuria, retention	Lateral to right ureter	Embryoma	?	Excision. Well—2 yrs.
1918	Lambrethsen[31]	M	33	Hematuria, dysuria	Superior wall	Round cell sarcoma	Regional lymph nodes	Died—days postoperative
1920	McKenna[32]	F	42	Hematuria—6 mos.	About left ureter	Spindle cell sarcoma	None	Excis., living when reported
1921	Stein[33]	M	55	Abdominal pain on urination	Left bladder roof	Sarcoma	?	Died—4 mos.
1923	Lowen[34]	F	20	Urinary retention—10 days	Neck of bladder	Round cell sarcoma	None	Died—1 mo.
1924	Leroux and Marion[35]	F	44	Hematuria, frequency	Multiple nodules	Plasmocytoma	?	Well—1 mo.
1925	Jamieson[36]	M	29	Retention, abdominal pain	Diffuse	Spindle cell sarcoma	None	Died—18 days, hydronephrosis
1925	Smith[37]	M	33	Retention, abdominal pain	Trigone—right lateral wall	Round Cell sarcoma	Local, muscle, jejunum, kidney	Died—3½ mos.
1925	Bottari[38]	F	16	Hematuria, abdominal mass	Diffuse	Spindle cell carcoma	?	Died—postoperative, renal insufficiency
1926	Cecil[39]	M	27	Hematuria, renal retention —6 mos.	Trigone, lateral and posterior walls	Fibroblastic sarcoma	None	Living—1 yr., cystectomy

TABLE III—(*Cont.*)

TABLE III—(*Cont.*)

Date	Author	Sex	Age	Symptoms	Location	Diagnosis	Metastases	Course
1926	Caulk[40]	F	71	Hematuria, pain in bladder—2 mos.	Dome of bladder	Spindle cell sarcoma	?	Died—4 mos., pneumonia
1926	Saturski[41]	F	33	Hematuria, frequency, burning, dysuria	Posteriorly left of midline	Fibromyxoma	Local recurrence	Living—10 mos.
1927	Marogna[42]	M	36	Hematuria, frequency, tenesmus	Posterior at base of dome	Lymphosarcoma	?	Died—postoperative
1927	MacKenzie and Chase[43]	F	69	Hematuria, abdominal pain	Trigone	Rhabdomyosarcoma	Lymph nodes, liver, duodenum	Died—6 mos.
1928	Garofalo[44]	M	51	Hematuria, frequency, tenesmus	Posterolateral wall	Angiosarcoma	?	?
1928	Weiss and Dreyfus[45]	M	6 mos.	Urinary obstruction, cachexia	Trigone, posterior wall	Myxosarcoma	Lung	Died—1 mo.
1928	Foulds[46]	M	74	Hematuria, pain, bladder spasm	?	Sarcoma	Local recurrence	Living when reported
1928	Bryan[47]	M	42	Hematuria, dysuria, tenesmus	Diffuse	Round cell sarcoma	None	Died—postoperative
1929	Hager and Hunt[48]	F	53	Hematuria—10 days	Posterior wall	Leiomyosarcoma	None	Living—4 yrs., cystectomy
1929	McCarthy, Stepita and Halperín[49]	M	48	Hematuria, nocturia burning	Posterior to trigone	Spindle cell sarcoma	?	Excision. Living—8 mos.
		M	4	Frequency, pain, dysuria—3 mos.	Left lateral wall	Spindle cell sarcoma	?	Died—4 mos.
1929	Descalopoulos[50]	?	9 mos.	Urinary obstruction, abdominal mass	Anterior wall	Myxoma	Peritoneal	Died—3 mos.
1929	Houette[51]	M	13 mos.	Frequency	Posterior and superior walls	Rhabdomyoma	?	Died—5 days, hydronephrosis
1929	MacKenzie and Hawthorne[52]	M	54	Hematuria, burning—1 wk.	Roof extending down to bladder neck	Round cell sarcoma	?	Excision and radiation. Living—10 mos.
1930	Smith[53]	M	48	Hematuria, nocturia kidney pain, weight loss	Left lateral wall	Spindle cell sarcoma	Local invasion	Died—6 wks.
1930	Caylor and Walters[54]	M	4	Hematuria, frequency, dysuria—8 mos.	Superior and antero-lateral walls	Leiomyosarcoma	?	Died—3 mos.
1931	Mintz[55]	M	5	Hematuria, frequency, dysuria, abdominal pain—4 mos.	Posterior inferior wall	Leiomyosarcoma	None	Died—1 yr.
1931	Dupont and Misrachi[56]	F	32	Hematuria, frequency, weight loss	Trigone and right lateral wall	Reticulolymphosarcoma	?	Excision. Living when reported

TABLE III—(*Cont.*)

Date	Author	Sex	Age	Symptoms	Location	Diagnosis	Metastases	Course
1932	Lazarus and Rosenthal[57]	M	2	Hematuria, frequency, tenesmus—4 wks.	Diffuse	Myxosarcoma	None	Died—11 mos.
1932	Eljasz[58]	M	16	Hematuria	Left lateral wall	Kaposi	?	Living
1932	Krauskopf[59]	F	60	Frequency, pain, abdominal mass	Diffuse	Leiomyosarcoma	?	Died—36 days, anuria
1932	Garvey and Barry[60]	F	13	Hematuria, frequency dysuria—4 wks.	Trigone and base	Spindle cell sarcoma	Local extension	Died—7 mos.
1932	Weiss and Meyer[61]	?	4½ mos.	Frequency, dysuria—1 mo.	?	Myxosarcoma	?	Died—1 wk., uremia
1932	Gazzolo[62]	M	61	Hematuria, frequency, dysuria	Trigone	Fusocellular sarcoma	?	Living when reported
1933	Czaykowski[63]	M	34	Hematuria, frequency—2 yrs.	Left upper wall	Polymorphofusocellular sarcoma	?	Excision. Living—3 mos.
1933	Krauskopf[64]	M	74	Hematuria, frequency, weight loss—5 wks.	Right lateral wall	Leiomyosarcoma	None	Died—5 mos.
1934	Harvey and Tennant[65]	F	1 mo.	Cachexia, pelvic mass	Trigone	Neurogenic sarcoma	None	Died—18 hrs.
1935	Jelm[66]	M	47	Hematuria, frequency, dysuria—2 mos.	Right posterior wall	Mixed cell sarcoma	?	Died—6 wks.
1935	Diaz Munoz[67]	M	63	Hematuria, dysuria, frequency—18 mos.	Diffuse	Polymorphocellular sarcoma	?	Died—days postoperative
1935	Kitagawa[68]	F	58	Hematuria, frequency—6 mos.	Posterior wall	Round cell sarcoma	None	Died—7 mos.
1936	Welfeld, Hill and Hillebrand[69]	?	?	Hematuria, incontinence, pain—5 mos.	Base	Rhabdomyosarcoma	?	Died—6 mos.
		M	2	Frequency, incontinence, straining—8 mos.	Anterior wall	Rhabdomyosarcoma	?	Died—weeks
1937	White and Gaines[70]	M	38	Hematuria, dysuria frequency, renal pain	Trigone over right ureter	Spindle cell sarcoma	?	Living, but failing rapidly
1937	Feggetter[71]	F	10	Hematuria—1 day	Fundus	Sarcoma	?	Excision. Living—1 yr.
1937	Weyerbacher and Balch[72]	M	4	Hematuria, frequency, retention, pain—1 wk.	Left lateral wall	Leiomyosarcoma	Lungs	Died—3 wks.
1938	Pich and Weber[73]	F	80	Hematuria, frequency	Trigone	Spindle cell sarcoma	None	Died—2 days postoperative
1938	Ashburn and Wollenweber[74]	M	59	Pain in bladder, nocturia, burning	Left lateral wall	Leiomyosarcoma	None	Died
1938	Registry[75]	M	72	Hematuria	Right lateral and posterior wall	Spindle cell sarcoma	?	Died—days postoperative
1938	Carver[76]	F	33	Hematuria	Superior wall	Leiomyosarcoma	?	?

TABLE III—(*Cont.*)

Date	Author	Sex	Age	Symptoms	Location	Diagnosis	Metastases	Course
1938	Hirsch and Brown[77]	M	72	Hematuria, frequency, dysuria—3 mos.	Diffuse	Myoblastic sarcoma	Lymph nodes, lung, liver and bone	Died—4½ mos.
1939	Burlakov[78]	F	54	?	Diffuse	Leiomyosarcoma	?	Died
1939	Cross[79]	F	50	Frequency, pain in bladder	Diffuse	Fibrosarcoma	Mesentery, colon	Died—10 days
		M	53	Hematuria, bladder pain—1 wk.	?	Round cell sarcoma	?	Excision. Living—1 yr.
1939	Uhlmann, Grossman and Calbin[80]	M	10 mos.	Pain on urination	Diffuse	Rhabdomyosarcoma	Local extension	Died—5 wks.
1939	Kretschmer and Doerhing[81]	M	55	Hematuria, frequency, dysuria, weight loss	Diffuse	Leiomyosarcoma	None	Died—5 mos.
1939	Ratliff and Valk[82]	M	65	Hematuria, frequency, incontinence	About left ureter	Rhabdomyosarcoma	None	Died
		M	6	Dysuria, frequency, straining—6 mos.	Vesicle neck	Rhabdomyosarcoma	Local extension	Died—8 mos.
		M	12	Frequency, straining—9 wks.	Vesicle neck	Myxofibrosarcoma	Local extension	Died postoperative
1939	Vermooten[83]	F	20 mos.	Hematuria, frequency, difficulty in urination	Trigone	Rhabdomyomyxosarcoma	None	Died—15 days, pneumonia, hydronephrosis
1939	Munger[84]	F	36	Hematuria, frequency, weight loss—5 wks.	Vertex of bladder	Leiomyosarcoma	Liver, intestine	Died—6 mos.
1940	Gayet[85]	M	62	Cystitis	?	Leiomyosarcoma	None	Died—4 mos.
		M	?	Hematuria	?	Leiomyosarcoma	None	Died—3 mos.
		M	?	Hematuria, frequency	Left bladder wall	Leiomyosarcoma	?	Died—1 mo., pyelonephritis
1940	Oetama[86]	M	40	Dysuria, frequency, abdominal swelling	Anterior and lateral walls	Polymorphocellular sarcoma	?	?
1941	Mingazzini[87]	M	38	Hematuria, frequency	Right posterior wall	Mixed cell sarcoma	?	?
1941	Keane[88]	F	17	Hematuria, dysuria—3 wks.	Right superior wall	Leiomyosarcoma	None	Excision. X-ray. Living 10 mos.
1941	Bugbee and Dargeon[89]	M	9 mos.	Hematuria, frequency, pain, retention	Left lateral wall	Sarcoma	None	Died—3 mos.
1941	Bonne[90]	M	58	Hematuria, frequency	Trigone	Myxofibrosarcoma	?	Died, pyelonephritis
1942	Kreutzmann[91]	F	47	Hematuria, frequency, cystitis—25 yrs.	Trigone between ureters	Lymphosarcoma	None	Excision. X-ray. Living—20 mos.

NOTE: Reports of cases recorded by Watkins[92], Montenegro[93], Tissot[94], Martelli[95], Okubo[96], Astraldi and Monserrat[97], Bongiorno[98], Wagner[99], and Price[100] were not available to us.

decade. The proportion of male to female cases is about 2:1, and this agrees with the statistics previously assembled by Cecil.[39]

Pathology: Grossly, the tumor may be either localized or diffuse. The vast majority of the localized tumors occurred in or about the trigone, frequently developing near one of the ureteral orifices. The diffuse growths also often involved the trigone and those tumors reported in Table II as being located elsewhere usually involved this structure as well. Many of the tumors have been polypoid or pedunculated, or started out in that form as did our case.

The histologic variants are indicated in Table II. The great bulk of the tumors are either leiomyosarcomata or fibrosarcomata, particularly if one includes the round, spindle and mixed cell types in this group. We believe they should be so considered. The most unusual cases reported have been the plasmocytoma recorded by Leroux,[35] an angiosarcoma reported by Garofalo,[44] and a case of multiple hemorrhagic sarcoma of Kaposi, published by Eljasz.[58] The carcinosarcomata have been purposely omitted because of the unsettled question as to the actual nature of their cellular components.

Diagnosis: The clinical aspects of the various sarcomata do not offer any differential points from the carcinomata of the bladder. Hematuria is an almost constant symptom (Table II), and it may be constant or intermittent, massive or slight. Dysuria, frequently with severe pain and frequency, are the next most frequent symptoms. Since the tumors grow rapidly, urinary obstruction develops early, so that varying degrees of frequency, incontinence and retention follow. Occasionally tissue fragments are passed in the urine and recognized.

The clinical diagnosis is simply that of bladder tumor, the diagnosis of sarcoma being entirely a histologic one.

Course: The tumors grow rapidly and infiltrate locally, so that the majority of the cases die in less than six months. It is interesting that so few of the cases have shown blood stream metastases, the more usual extension being through the bladder and neighboring tissues. Involvement of one or both ureters is almost constant, so that hydronephrosis, pyelonephritis and nitrogenous retention usually occur and are frequently the immediate cause of death along with cachexia.

Therapy has been attempted by both complete cystectomy and radium and roentgenotherapy. Several cases have survived for one year, as shown by the reports assembled in Table III, but to date no five-year cures have been reported. Since metastases occur by local extension and infrequently by the blood stream, complete cystectomy, as suggested by Cecil,[39] should be attempted wherever possible.

SUMMARY

1. A case of primary osteogenic sarcoma of the bladder containing large amounts of alkaline phosphatase histologically and showing a range of phosphatase activity identical with that of primary osteogenic sarcomata of bone is recorded.

2. The possible origin of osteogenic tumors of the bladder from urinary epithelium (metaplasia) and embryologic rests (wolffian body) is discussed.

3. A high alkaline phosphatase content in a tumor by chemical and histochemical methods, while characteristic of osteogenic sarcomata, should not be regarded as diagnostic until we have further knowledge of the phosphatase activity of tumors derived from cells normally rich in phosphatase, as those of bladder mucosa and kidney.

4. The literature of sarcoma of the bladder has been reviewed and the characteristics of the various sarcomata of the bladder outlined.

5. Sarcoma of the bladder occurs in all age-groups, but with peaks in early and later life. Histologically, the tumors are most frequently fibrosarcomata or leiomyosarcomata, or variants of these.

6. The diagnosis of sarcoma of the bladder is entirely a histologic one.

7. At present, radical and complete cystectomy offers the only chance of a cure.

We are indebted to Dr. H. Q. Woodard of Memorial Hospital, N. Y. C., for the phosphatase studies on this tumor; to Dr. A. P. Stout of the College of Physicians and Surgeons, N. Y. C., for his interest and suggestions, and to Misses Edith Carney and Antoinette DeVito of St. John's Hospital, Brooklyn, for their invaluable technical assistance.

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MENINGIOMA

CASE REPORT

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TO REPORT a single case of so common a lesion as a meningioma would be unjustifiable were it not that I believe the tumor in question to be the largest intracranial neoplasm ever reported. Removal of the mass was successfully carried out and recovery was uneventful. In addition, the case illustrates the preponderance of symptoms referable to structures in the posterior fossa which may sometimes accompany a mass on the superior surface of the tentorium cerebelli.

Case Report.—V. U. Hosp. No. 116805: J. L. O., white, male, age 25, was referred by Dr. F. H. Booher, of Lynchburg, Tenn., September 16, 1941, because of headaches and failing vision.

For many years he had suffered from repeated attacks of bronchial asthma, sometimes requiring epinephrine for relief. Three years before admission, he was jaundiced for a few days. There had been no other significant illnesses or injuries. One grandmother had suffered from mental disease of unknown nature.

Fifteen months prior to admission, he began to have bitemporal or generalized headaches of slowly increasing frequency and duration. Three months later, the headaches were sometimes associated with vertigo and occasional vomiting, and he began to be unsteady in walking. For eight months, he had noted progressive loss of hearing in the right ear, without tinnitus, some impairment of his sense of taste ("sweet things taste bitter"), intermittent difficulty in swallowing, and occasional hoarseness. During the two months prior to admission, his vision had failed rapidly in both eyes.

Physical Examination.—The patient was alert and cooperative. Memory and speech were normal. His neck was stiff, and his head was held in a retracted position. Vision was limited to perception of moving fingers at two feet. The visual fields could not be determined. The pupils reacted normally. There was marked bilateral papilledema, with advanced secondary optic atrophy. A slow, coarse nystagmus was present on lateral gaze to either side, equal in each direction. The fifth and seventh cranial nerves were unaffected. Hearing tests showed that air conduction was almost *nil*, and bone conduction greatly reduced on the right. The Weber was referred to the left. The gag reflex was not obtained on either side, but pharyngeal sensation seemed normal. Swallowing, phonation and tongue movements were normal at the time of examination.

Strength was equal on the two sides, and no loss of sensation was found. The reflexes were normal and equal. Babinski's sign was not present. There was no clonus. Coordination was good in the upper extremities but the patient walked with a broad base and was very unsteady. He veered to the right and tended to fall to the right.

There was a pigmented mole over the sternum, and a small, firm, subcutaneous nodule, possibly a neurofibroma, just below the left clavicle.

Laboratory observations were noncontributory. Roentgenograms showed marked thinning of the entire skull with greatly increased "convolutional" markings. In the the region of the lambdoidal suture on the right was an area of thickening, suggestive of hyperostosis, but there was no surrounding increase in vascularity. All sutures

were markedly separated. The sella turcica was larger than normal and the dorsum sellae was eroded. There was modernate erosion of the petrous ridge on the right.

The tentative preoperative diagnosis was right acoustic tumor, but because of atypical features ventricular estimation and, subsequently, ventriculography were carried out. Ventriculograms showed the right ventricle displaced anteriorly and flattened on its posterior aspect, evidently by a right occipital mass (Fig. 1). Removal of the lesion was undertaken immediately.

Operation.—September 25, 1941: Under intratracheal ether anesthesia, a large osteoplastic flap was turned down in the right occipital region, extending to the lateral sinus posteriorly and almost to the longitudinal sinus medially. The bone was exceedingly

FIG. 1.—Ventriculogram showing the anterior displacement and posterior compression of the right ventricle by the enormous tumor in the right occipital region.

thin (indeed, in several spots, its entire thickness was eroded) except in the thickened area seen in the roentgenograms. This area was slightly adherent to the dura, but was easily separated. When the flap was reflected, the adherent area of dura was seen to show the characteristic radial "puckering" indicating an underlying meiningioma.

A circular incision was made in the dura to include the adherent area and the remainder of the dural flap was reflected separately, leaving this area attached to the enormous tumor which was thus brought into view. An area of tumor-surface about five centimeters in diameter was exposed. Numerous large vessels connected it with the surrounding cortex laterally and anteriorly. Gentle dissection posteriorly and medially showed no invasion of, or direct attachment to, the great dural sinuses. The superficial vascular connections were coagulated or clipped and divided, and the dissection of the cortex from the surface of the tumor begun. It became apparent immediately, however, that the mass extended so far beneath the brain that it could not be removed intact without irreparable damage. Accordingly, with the electrosurgical loop, a large intracapsular excavation was produced. This greatly reduced the size of the lesion and allowed partial collapse of its walls. It was then possible gradually to enucleate the remaining mass intact. Deeper vascular attachments were troublesome, but were secured without excessive difficulty. The central defect in the dura was left open, the wound closed, and the patient given a transfusion.

Postoperative Course.—Recovery was uneventful except for some temporary accu-

mulation of cerebrospinal fluid (which had escaped through the dural defect) under the scalp. When discharged, on the 27th postoperative day, he walked with evidence of weakness, but without staggering.

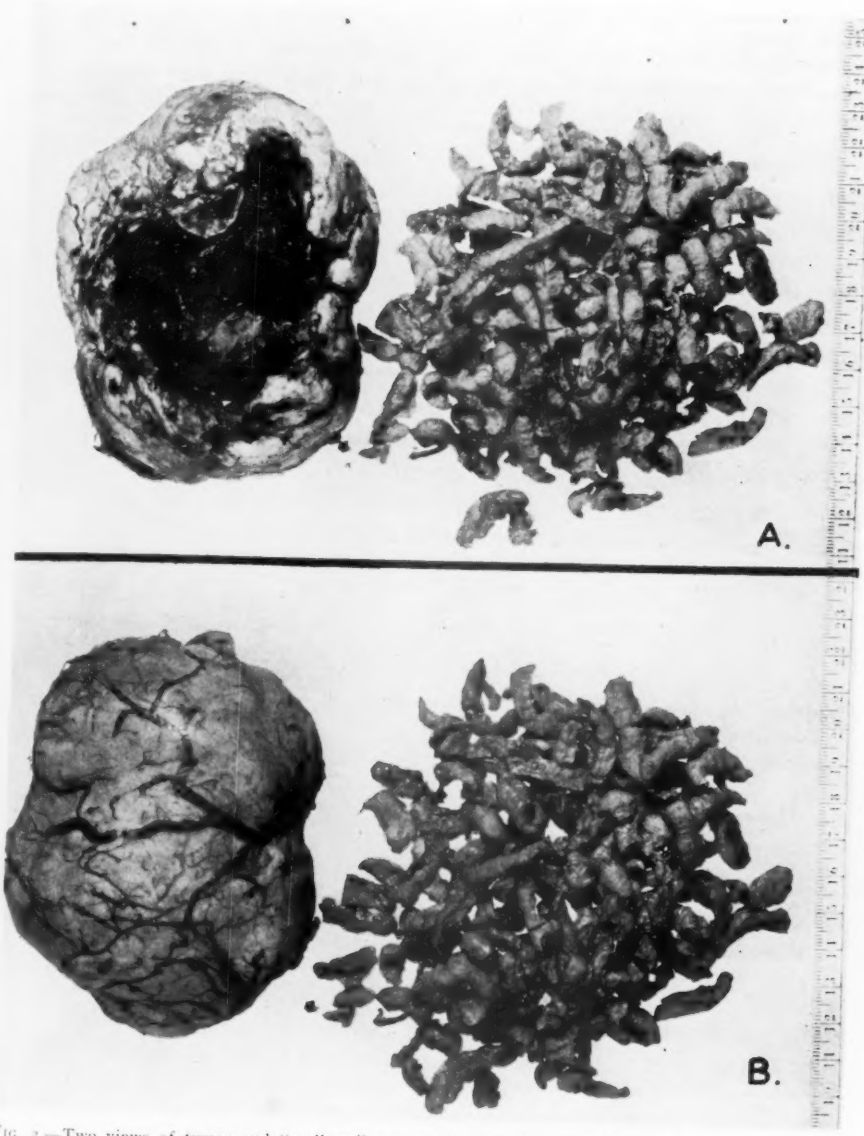

FIG. 2.—Two views of tumor and "scallops," removed by the electrosurgical loop. A. The presenting surface with excavation. B. The deep surface which lay on the tentorium.

Immediately after operation, he was unable to perceive light, but at discharge he could count fingers at three feet. Four months later, the vision in the right eye was 2/200, and ten months after discharge it was 5/200 in each eye. At the last examination, 20 months after operation, the vision was unchanged, and there was marked secondary optic atrophy. No other symptoms or signs were present.

Pathologic Examination.—Gross: The tumor (Fig. 2) was nearly spherical, with a diameter of 12 cm. Its weight was 374 Gm. The capsule was smooth, thick and intact except at the area of excavation (which had included the dural attachment). The tumor substance was firm, slightly granular in appearance, and apparently perfectly uniform throughout.

Microscopically, the tumor was a typical meningioma of fibroblastic type. The elliptical cells were arranged in parallel streams and whorls and were supported by a fine collagenous network. It was very vascular. Very rare mitotic figures were seen.

Comment.—The frequency with which the slowly growing meningiomata attain great size has been discussed in many publications. Cushing and Eisenhardt[1] cite numerous reports of large tumors, the largest of which was the otherwise unpublished 341 Gm. meningioma removed by Hoen. The largest in Cushing's series of 313 meningiomata weighed 310 Gm.* Davidoff[2] removed, in three stages, masses of tissue aggregating 835 Gm., but this included an enormous hyperostosis of the skull.

So far as I am aware, therefore, the meningioma reported herein exceeds in size any primary intracranial tumor previously removed.

As already mentioned, the symptoms in this case were, for the most part, referable to the posterior fossa and were probably attributable to compression and displacement of the cerebellum and brain stem by the huge mass lying on the superior surface of the tentorium.

SUMMARY

The successful removal of a meningioma weighing 374 Gm. is reported.

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* At several secondary operations, Cushing removed recurrent masses of tumor exceeding 400 Gm.

ANTERIOR SACRAL MENINGOCELE

REPORT OF THREE CASES

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ANTERIOR SACRAL MENINGOCELE is of sufficient rarity to warrant the report of another case successfully removed surgically. Two other cases, untreated, are included in this report. Coller and Jackson[1] have reviewed the literature and have reported their case, with a description of the operative treatment employed.

In summarizing the article of Coller and Jackson, only 23 cases, including their own, were found in the literature. Their case made a complete recovery after surgical treatment. Of the remaining cases reported in the literature,

FIG. 1.—Case 1: Roentgenogram showing absence of sacrum on left. Air in bowel obscures first and second sacral segments.

18 were treated, with a mortality of 44 per cent. Of these 18, eight were cured, and two remained the same. The first case was described by an anonymous surgeon in 1837. The ratio of occurrence was of 20:3 females to males. Most of the cases occurred in the second and third decades of life, and commonly were found as complications of menstrual disturbances and of pregnancy. Attempts to open the tumor through the vagina met with death from meningitis (Kroner, in 1881, and Thomas, in 1885). The first successful operative approach was in 1903, by Pupovac, who employed a dorsal incision, exposed the tumor, resected part of its wall, and closed the remainder of the sac upon itself with sutures. Grossman, in 1906,

exposed the pedicle of the tumor through a posterior incision and sutured it to the periosteum of the sacrum. Coqui, in 1916, and Roux, in 1918, both exposed the pedicle of the sac at celiotomy and ligated it, with resultant cure. In 1929, Drennan employed the posterior approach unsuccessfully. In 1938, Santy, through a posterior approach, removed the meningocele and

FIG. 2.—Case 2: Roentgenogram showing markedly deformed sacrum and lower lumbar vertebrae.

two dermoids. A cerebrospinal fluid fistula drained for six months, but the patient made a good recovery.

In the case reported by Coller and Jackson, a retroperitoneal tumor of other origin was suspected preoperatively. The tumor was first approached through the abdomen, but because the exposure was inadequate, the patient was placed in the prone position, and through a posterior incision just lateral to the midline the tumor was exposed and the pedicle ligated with silk. The sac was left intact after it had been aspirated. No nerves were found within the sac. A small pack was left against the ligated pedicle and brought out through the wound. Postoperatively, the hips were kept elevated above the level of the shoulders for six days, and the foot of the bed elevated for about 13 days. The wound healed in 41 days.

Of the three cases herein reported, only one complete history and operative procedure is available (Case 3). Cases 1 and 2 did not come to surgery, and are reported through the courtesy of Dr. Don King.

CASE REPORTS

Case 1.—G. McW., white, female, age 50, married, entered the hospital in March, 1940, with the complaint of pain in the back and shortness of breath. For several years before entry, she had been followed with no particular complaint except for occasional pains in both legs. Frequent examinations during this period were unrevealing. Three months before entry, she had had pneumonia. There was no history of rheumatic fever. She had borne children without difficulty.

Physical Examination.—Temperature was 38.2° C., pulse 140, respirations 30. Blood pressure 160/60. She was pale, and her back could hardly be touched because

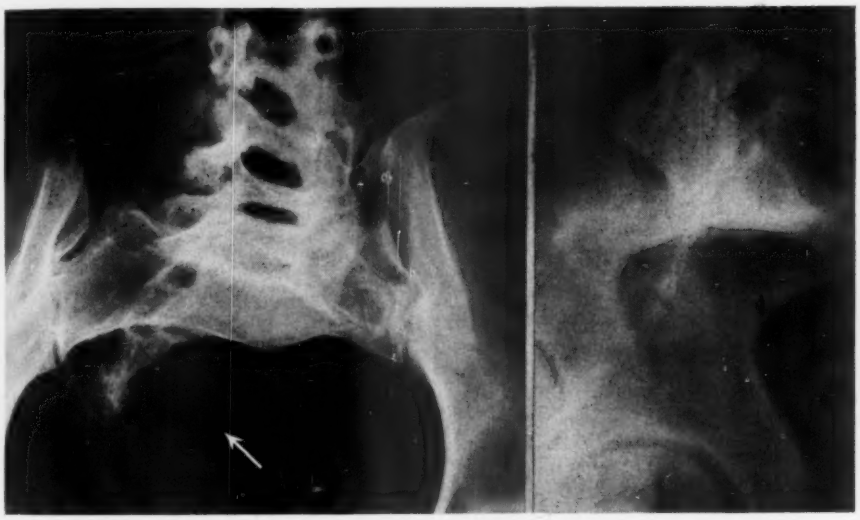

FIG. 3.—Case 3: Anteroposterior and lateral roentgenograms showing marked defect of left portion of sacrum.

of severe pain. Positive physical findings included râles over both lung fields, posteriorly. A diastolic murmur was heard along the left sternal border and at the aortic and pulmonic areas. A large, smooth tumor was palpable in the left pelvis, on rectal examination. A roentgenogram of the sacrum showed a complete absence of the sacrum on the left (Fig. 1). Successive blood cultures showed 50 to 200 colonies of hemolytic streptococci. Numerous other laboratory studies were made in relation to her septicemia.

Thinking that the pelvic mass might be an abscess, she was operated upon for incision and drainage. The tumor was approached through the left buttock, but when it was seen that the subcutaneous tissues were not edematous, aspiration through the incision yielded no pus. The wound was closed. Aspiration was then done through the sacral defect, and cerebrospinal fluid was obtained. The pelvic mass disappeared following the aspiration.

Her blood cultures remained consistently positive until a few days before death, in spite of chemotherapy and transfusions. Her temperature varied between 38° C. and 39.5° C. She died 18 days after admission to the hospital.

Case 2.—T. T., white, male, age 29, entered the Bone and Joint Service in

October, 1940, for correction of a chronic ulceration of the skin over the cuboid bone of his right foot.

He had been born with a soft tumor over his sacrum, but without other noticeable deformity. He was normal throughout infancy until the age of four when he had a serious prolonged illness, diagnosed as "cholera morbus," characterized by severe diarrhea and high fever. After this illness, he had difficulty in walking. It was noted that he had a "stamping" gait with the left foot, and that the right ankle turned completely over so that he walked on the lateral side of the foot. During the course of the illness, urinary incontinence developed which persisted until he was 14 years old. Since that age, he had regained control of his urination, but had had frequency. Urethral dilatation a year before entry markedly improved his frequency. Since the boyhood illness he had had numerous pressure sores over his ischiae and over the lateral side of his right foot.

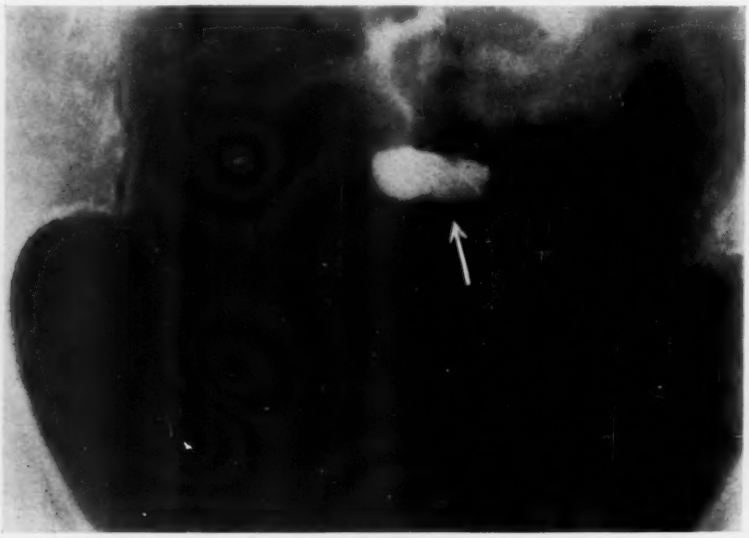

FIG. 4.—Case 3: Spot fluoroscopic film; Anteroposterior view of lumbosacral region just after lipiodol injection. Lipiodol outlines caudal portion of subarachnoid space, but does not enter meningocele.

Physical Examination.—Anal sphincter tone was present, but thought to be diminished. There was a soft semifluctuant mass, about 10 cm. in diameter, over the left side of the buttocks, overlying a palpable defect in the left side of the sacrum. The mass was also felt rectally. Pressure over the mass produced a headache. The right leg was in marked equinovarus, with weight-bearing upon the cuboid bone. The right foot was in marked calcaneocavus position. Hypesthesia was present only over the feet and perineum.

A roentgenogram showed malformation of the entire sacrum (Fig. 2). Osteomyelitis of the right cuboid bone of the foot was also noted. Aspiration of the sacral mass was not attempted. Since he had no symptoms referable to his meningocele, no surgical treatment was advised. His right leg was amputated below the knee. He made a good recovery from this operation.

It should be noted that the meningocele was palpable posteriorly as well as rectally in Case 2. The osseous anomaly involved the entire sacrum and lower lumbar vertebrae in this case.

Case 3.—H. E., white, female, age 29, unmarried, entered the hospital in September,

1942, complaining of lifelong constipation. She sought medical advice when laxatives no longer had effect. She had no other symptoms of rectal disease. She had always been healthy, otherwise. Her menarche was at 11 years. Menstrual periods were regular every 28–30 days, lasting 5–6 days, with severe dysmenorrhea during the first two days of the period.

Physical Examination.—No tumor was palpable abdominally. Pelvirectal examination revealed a huge mass which completely filled the left pelvis, crossing the midline. The rectal mucosa was freely movable over it, and the mass was slightly compressible. The rectum was displaced to the right. The uterus was anterior and small. There were no adnexal masses or tenderness.

Roentgenograms of the lower lumbar spine and pelvis showed a congenital absence of the left portion of the sacrum (Fig. 3). There were also anomalies of the 4th and 5th lumbar vertebrae. The radiologists detected the pelvic mass and suggested that it might be meningocele. The mass was further outlined with a barium enema which showed the rectum to be displaced to the right and upwards.

A lumbar puncture needle was inserted into the mass just to the left of the palpable bony sacrum. About 200 cc. of cerebrospinal fluid was obtained without discomfort

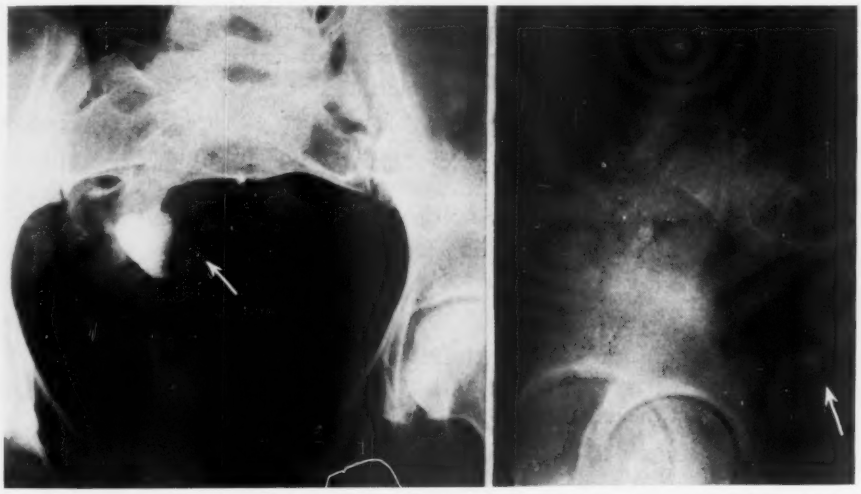

FIG. 5.—Anteroposterior and lateral views of pelvis, two weeks after introduction of lipiodol into subarachnoid space. All of lipiodol is in the meningocele. A few particles of lipiodol remain in spinal canal.

to the patient. The mass disappeared after aspiration. The following day a lumbar puncture was done without difficulty, and 1 cc. of lipiodol was introduced into the subarachnoid space. Fluoroscopic examination showed the lower portion of the dural sac to be flattened as though pushed upon by a mass (Fig. 4). None of the lipiodol was seen to enter the mass or leave the spinal canal (Fig. 4). Fluoroscopic examination was done the following day, and the lipiodol still remained in the spinal canal. Two weeks later, all of the lipiodol was in the pelvic mass (Fig. 5). The diagnosis of anterior meningocele was thus confirmed. All of these procedures were accomplished in the Out-patient Department, with no discomfort to the patient except for low back pain while the lipiodol remained in the spinal canal.

About a month later the meningocele was approached through a posterior incision beginning over the 4th lumbar vertebra and carried down over the sacrum. After division of the fascia over the defect in the sacrum, a tumor, about 14 cm. in diameter, presented itself. The patient's head and spine were lowered beneath the level of her hips. The sac was opened. No nerve elements were seen within it. The empty sac was then

completely dissected free of the pelvic viscera. At its caudal portion, two nodular structures were encountered which were thought to be coccygeal glands. These were cauterized with 95 per cent alcohol. The neck of the sac was small and the actual openings into the spinal canal was two and less than one millimeter in diameter. After amputation of the sac, the openings into the spinal canal were closed with mattress sutures of silk. The head of the table was elevated above the level of the hips. No fluid was seen to emerge from the suture line. The dead space was filled with normal saline, and the wound was closed with double medium silk sutures. The wound was dressed without pressure. A transfusion of 500 cc. of citrated blood was administered during the procedure.

Postoperatively, she was given a low-residue diet. The foot of the bed was elevated for about ten days. On the 10th postoperative day she developed infection in the dead space. This was drained through the wound. Her temperature gradually subsided to normal. She was dismissed on her 18th postoperative day. She had no signs of meningeal irritation at any time. Her wound had healed by the 31st day, and she had returned to work on the 33rd day after operation. Six months after operation, she felt well, was normally active, and had little trouble with constipation.

SUMMARY

1. Anterior sacral meningocele is a rare congenital anomaly associated with congenital absence of half of the sacrum.

2. Symptoms due to anterior sacral meningocele are those produced by pressure of the tumor upon pelvic viscera, or displacement of the latter by the tumor.

3. Until recent years, operative treatment of anterior sacral meningocele has been attended by high mortality from meningitis.

4. Successful removal of an anterior sacral meningocele is achieved through a posterior approach.

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[1] Coller, F. A., and Jackson, R. G.: Anterior Sacral Meningocele. Surg., Gynec. and Obst., **75**, 703, June, 1943.

BOOK REVIEW

ENDOSCOPIC PROSTATIC SURGERY. By Roger W. Barnes, M.D. St. Louis: C. V. Mosby Co., 1943.

The terms employed in urologic surgery seem to be constantly undergoing change. Though it is barely thirty years since the operation with which this monograph is concerned was first introduced, it seems always to be assuming new titles. We have heard it called "transurethral," "interurethral," "intra-urethral," or "*per urethram*." Again, it is "intervention upon the prostate by the endoscopic route," or perhaps "endoscopic excision." The title Dr. Barnes has chosen is perhaps, as good as any—if not better than most—and it is to be hoped may prove sufficiently authoritative to provide a permanent standard term designating this particular procedure.

The historical section is unimportant and might be passed over were it not that it seems necessary to remark that the selection of *what was to be left out* might have been made with more wisdom and accuracy. The "Foreword," likewise, fails to give credit to several of the chief pioneers, whose work contributed so much to the present high standing of the operation, both as to mechanical equipment and operative technic. It was the men who never let their enthusiasm run away with their reasoned judgment, who were able to evaluate, truly, the proper place of endoscopic resection, so as to make use of it *only* when all the circumstances combined to make that use logical, or even inevitable, who really brought the procedure to general acceptance.

There is no doubt, in the reviewer's mind, that prostatic resection has come to stay, and is in no wise a fad of the extremists. But not until *all* urologic surgeons realize that it is applicable only in carefully selected cases, and should never be undertaken routinely, whether or not the patient would be better served by some other type of intervention, that it will come to full usefulness. The technic selected should be that best suited to the pathologic findings in any given case, and not the operation the surgeon is most skilful in performing. To perform the endoscopic procedure properly requires exactly as much study and practice as is necessary for the suprapubic or perineal routes, as Dr. Barnes most properly emphasizes, and no man is a competent surgeon unless he can perform all three with equal precision and success.

Along the Eastern seaboard the proportion of excisions *per urethram* to the two other types of procedure seems better balanced than in the farther West. Our western colleagues seem to be still sharply divided—one faction being extremely conservatives, while the other proclaims, on all occasions, that large numbers—if not hundreds—of endoscopic resections have been performed upon patients of all ages, with prostates in all stages of hypertrophy, with almost 100 per cent perfect results, and fewer deaths than follow the older procedures.

Dr. Barnes, however, joins neither faction. He feels that a levelling-off process has been for some time at work and that the indications for the use of the endoscopic route can be set up definitely by a rule far more accurate than that of-thumb. The number of "recurrences" presented in the larger medical centers for reoperation, attest, only too eloquently, how often the method is unwisely employed, and by those who have not acquired sufficient skill to perform it properly, even when the indications point unerringly to the employment of the endoscopic route.

The chapter on anatomy and pathology is clear and concise; the section on the prostatic blood supply being especially well illustrated and described. Appropriate emphasis is laid on the likelihood and dangers of hemorrhage. The whole area is often so hemorrhagic that it is impossible to pick out the individual bleeding vessels and cauterize them separately. If a "mass" cauterization is given to all the tissue cut, deep sloughing is almost sure to result, so that the necrosis is as extensive and dangerous as in other technics, which have been criticized on that account.

Most excellent is the chapter on electric current modifiers. It might well be thoughtfully read by every urologist who takes up this type of practice. Because at least 50 per cent of his success depends upon his mechanical equipment, the most finished operator will be helpless if his machine fails.

Of the portion of the book dealing with punch instruments, the reviewer does not feel qualified to speak, because he is unfamiliar with this equipment. This is due to the fact that he has found instruments of the McCarthy type, with the fore-oblique lens system afford clear visualization at all times, making the "blind" maneuvering with this type of punch a most unsatisfactory procedure. Dr. Barnes' description of his technic is brief, clear, and to the point, and his consideration of possible emergencies, good. There has never yet been an operator so skilful or *lucky* that he has not been faced with some of the accidents here enumerated. Injury to the external sphincter is perhaps the worst that may befall—from the patient's viewpoint at least—and the precautions mentioned should be scrupulously observed. The book offers many valuable suggestions.

THOMAS J. KIRWIN.

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